P, ENT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 05 June 1997 (05.06.97)	
International application No.: PCT/AU96/00767	Applicant's or agent's file reference:
International filing date: 29 November 1996 (29.11.96)	Priority date: 30 November 1995 (30.11.95)
Applicant: PANACCIO, Michael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

30 April 1997 (30.04.97)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1868774/EJH/AF	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU 96/00767**	International filing date 29 November 1996	Priority Date 30 November 1995

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[6] C12N 15/31; A61K 39/02; A61K 39/106

Applicant

(1) DARATECH PTY LTD et al.

(2) PANACCIO, Michael et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 7 sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[X]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand 30 April 1997	Date of completion of the report 14 August 1997
Name and mailing address of the IPEA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (06) 285 3929	Authorized Officer **S.D.BARKER** Telephone No. (06) 283 2294

INTERNATIONAL PRELIMINARY EXAM TION REPORT

Int[redacted]ional application No.
PCT/AU 96/00767

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages **1-31, 33-72,** as originally filed,
pages , filed with the demand,
pages **32, 32A, 32B,** filed with the letter of **22 January 1997 ,**
pages , filed with the letter of .

☒ the claims, Nos. **1-90,** as originally filed,
Nos. , as amended under Article 19,
Nos. , filed with the demand,
Nos. , filed with the letter of ,
Nos. , filed with the letter of .

☒ the drawings, sheets/fig , as originally filed,
sheets/fig , filed with the demand,
sheets/fig **1-4,** filed with the letter of **22 January 1997,**
sheets/fig , filed with the letter of .

2. The amendments have resulted in the cancellation of:

☒ the description, pages **32**

☐ the claims, Nos.

☒ the drawings, sheets/fig **1-4**

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

Please note that claims 32-62 include subject matter falling within Rule 67.1 and as such do not require an International Preliminary Examination. However, as these claims do not contravene Australian law they have been considered in the examination.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☒ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**3-5, 8-9, 12-62, 65-76, 79-90**	**YES**
	Claims	**1-2, 6-7, 10-11, 63-64, 77-78**	**NO**
Inventive step (IS)	Claims	**1-90**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1-90**	**YES**
	Claims		**NO**

2. Citations and explanations

NOVELTY (N): Claims 1-2, 6-7, 10-11, 63-64, 77-78

Citations

(a) AU 69290/94 A (Institut Pasteur et al.,) 12 December 1994

(b) Suerbaum et al., "*Helicobacter pylori* hspA-hspB heat-shock gene cluster: nucleotide sequence, expression putative function and immunogenicity", Molecular microbiology, Volume 14, No. 5, 1994, pages 959-974, see entire document

(c) Wu et al., "Heat Shock-and Alkaline pH-Induced Proteins of *Campylobacter jejuni*: Characterisation and Immunological Properties", Infection and Immunity, Volume 62, No. 10, 1994, pages 4256-4260, see entire document

(d) Dunn et al., "Identification and Purification of a cpn 60 Heat Shock Protein Homolog from *Helicobacter pylori*", Infection and Immunity, Volume 60, No. 5, 1992, pages 1946-1951, see entire document

(e) Evans et al., "Urease-Associated Heat Shock Protein of *Helicobacter pylori*", Infection and Immunity, Volume 60, No. 5, 1992, pages 2125-2127, see entire document

(f) Takata et al., "The Purification of a GroEL-Like Stress Protein from Aerobically Adapted Campylobacter jejuni", Microbiol Immunol, Volume 39, No. 9, pages 639-645, see entire document

(g) Bukanov et al., "Ordered cosmid library and high-resolution physical-genetic map of *Helicobacter pylori* strain NCTC11638", Molecular Microbiology, Volume 11, No. 3, 1994, pages 509-523

Citations (a) and (b) disclose immunogenic compositions from *Helicobacter pylori* (previously Campylobacter). These documents also disclose nucleic acid molecules encoding Heat Shock Proteins (HSP's) and the Heat Shock Proteins.

Citation (c) discloses immunogenic HSP's from *Campylobacter jejuni* having homology with GroEL and GroEs.

Citation (d) discloses a *H Pylori* urease having homology with GroEL.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of : Box V

Citation (f) discloses a *C jejuni* protein having homology with GroEL.

Citation (g) discloses the gene sequence for GroEL.

The present application states that *Lawsonia intracellularis* is a *Campylobacter*-like organism (page 2, lines 12-13). Hence, it would seen claims 1-2, 6-7 and 10-11 may encompass immunogenic components from *Campylobacter* or *Helicobacter* species as disclosed in the citations. A carrier or diluent may encompass a simple aqueous solution.

Claims 63-64 and 77-78 are anticipated by the cited nucleic acids encoding the cited proteins as these would appear to be homologous with the nucleic acids of SEQ IDS 1 and 3.

Please note that the following document was identified in the international search as being an "X" document but was, in fact, published after the priority of the present application:

- Kansau et al., "Heat shock proteins of *Helicobacter pylori*", Aliment Pharmacol Ther, Volume 10, Suppl 1, 1996, pages 51-6, see entire document.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

HUGHES, E., John, L.
Davies Collison Cave
1 Little Collins Street
Melbourne, VIC 3000
AUSTRALIE

Date of mailing (day/month/year) 05 June 1997 (05.06.97)	
Applicant's or agent's file reference	**IMPORTANT NOTICE**

International application No.	**International filing date** (day month year)	**Priority date** (day month year)
PCT/AU96/00767	29 November 1996 (29.11.96)	30 November 1995 (30.11.95)

Applicant
DARATECH PTY. LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,CZ,DE,EP,FI,IL,JP,KP,KR,NO,PL,RO,SK,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,DK,EA,EE,ES,GB,GE,HU,IS,KE,KG,KZ,LC,LK,LR,LS,LT,
   LU,LV,MD,MG,MK,MN,MW,MX,NZ,OA,PT,RU,SD,SE,SG,SI,TJ,TM,TR,TT,UA,UG,UZ,VN

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   05 June 1997 (05.06.97) under No. WO 97 20050

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PN6910/95, 6911/95/EJH/AF	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. **PCT/AU 96/00767**	International filing date *(day/month/year)* 29 November 1996	(Earliest) Priority Date *(day/month/year)* 30 November 1995

Applicant
(1) Daratech Pty. Ltd. et al.
(2) PANACCIO et al.

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **4** sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I)

2. [ ] **Unity of invention is lacking** (See Box II)

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   - [X] filed with the international application
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed
   - [ ] transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No.

   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure
   - [ ] because this figure better characterises the invention
   - [X] None of the figures

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00767

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C12N 15/31, A61K 39/02, A61K 39/106

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC C12N 15/31, A61K 39/02, A61K 39/106

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU:IPC (as above)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent, Chemical Abstracts: lawsonia, intracellularis, ileal, groel,groes, chaperonin
STN: nucleotide/amino-acid search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU, 69290/94, A (Institut Pasteur et al.) 12 December 1994	1, 2, 6, 7, 10, 11, 63, 64, 77, 78
X	Suerbaum et al., "*Helicobacter pylori* hspA-hspB heat-shock gene cluster: nucleotide sequence, expression putative function and immunogenicity", Molecular Microbiology, Vol. 14, No. 5, 1994, pages 959-974, see entire document.	1, 2, 6, 7, 10, 11, 63, 64, 77, 78

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 1997	26 FEB 1997
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929	Authorized officer **R.L. POOLEY** Telephone No.: (06) 283 2242

PCT/INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00767

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Kansau et al., "Heat shock proteins of *Helicobacter pylori*", Aliment. Pharmacol. Ther., Vol. 10, Suppl. 1, 1996, pages 51-6, see entire document.	1, 2, 6, 7, 10, 11, 63, 64, 77, 78
X	Wu et al., "Heat Shock- and Alkaline pH-Induced Proteins of *Campylobacter jejuni*: Characterization and Immunological Properties", Infection and Immunity, Vol. 62, No. 10, 1994, pages 4256-4260, see entire document.	1, 2, 6, 7, 10, 11, 63, 64, 77, 78
X	Dunn et al., "Identification and Purification of a cpn 60 Heat shock Protein Homolog from *Helicobacter pylori*", Infection and Immunity, Vol. 60, No. 5, 1992, pages 1946-1951, see entire document.	63, 77
X	Evans et al., "Urease-Associated Heat Shock Protein of *Helicobacter pylori*", Infection and Immunity, Vol. 60, No 5, 1992, pages 2125-2127, see entire document.	63, 77
X	Takata et al., "The Purification of a GroEL-Like Stress Protein from Aerobically Adapted *Campylobacter jejuni*", Microbiol. Immunol., Vol. 39, No. 9, pages 639-645, see entire document.	63, 77
X	Bukanov et al., "Ordered cosmid library and high-resolution physical-genetic map of *Helicobacter pylori* strain NCTC11638", Molecular Microbiology, Vol. 11, No. 3, 1994, pages 509-523.	63, 77

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU 96/00767

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU, A	69290/94	WO,	94/26901	EP,	703981	CA,	2144307
		JP,	8510120				

END OF ANNEX

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/31, A61K 39/02, 39/106

A1

(11) International Publication Number: **WO 97/20050**

(43) International Publication Date: 5 June 1997 (05.06.97)

(21) International Application Number: PCT/AU96/00767

(22) International Filing Date: 29 November 1996 (29.11.96)

(30) Priority Data:
PN 6910 30 November 1995 (30.11.95) AU
PN 6911 30 November 1995 (30.11.95) AU

(71) Applicants *(for all designated States except US)*: DARATECH PTY. LTD. [AU/AU]; 3rd floor, 493 St. Kilda Road, Melbourne, VIC 3004 (AU). PIG RESEARCH AND DEVELOPMENT CORPORATION [AU/AU]; Industry House, 3rd floor, Brisbane Avenue, Barton, ACT 2600 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PANACCIO, Michael [AU/AU]; 122 Hill Road, North Balwyn, VIC 3104 (AU). HASSE, Detlef [AU/AU]; 4 Scullin Court, Sunbury, VIC 3429 (AU).

(74) Agents: HUGHES, E., John, L. et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, VIC 3000 (AU).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: THERAPEUTIC AND DIAGNOSTIC COMPOSITIONS

(57) Abstract

The present invention relates generally to therapeutic compositions for the treatment and/or prophylaxis of intestinal disease conditions in animals and birds caused or exacerbated by *Lawsonia intracellularis* or similar or otherwise related microorganism. The present invention also contemplates methods for the treatment and/or prophylaxis of such intestinal disease conditions and to diagnostic agents and procedures for detecting *Lawsonia intracellularis* or similar or otherwise related microorganism.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
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THERAPEUTIC AND DIAGNOSTIC COMPOSITIONS

The present invention relates generally to therapeutic compositions for the treatment and/or prophylaxis of intestinal disease conditions in animals and birds caused or exacerbated by *Lawsonia intracellularis* or similar or otherwise related microorganism. The present invention also contemplates methods for the treatment and/or prophylaxis of such intestinal disease conditions and to diagnostic agents and procedures for detecting *Lawsonia intracellularis* or similar or otherwise related microorganism.

Bibliographic details of the publications numerically referred to in this specification are collected at the end of the description. Sequence Identity Numbers (SEQ ID NOs.) for the nucleotide and amino acid sequences referred to in the specification are defined following the bibliography.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

The meat industry in Australia and, indeed, in most countries of the world, is an important aspect of the overall livestock industry. However, the meat industry is subject to rapid economic downturn in response to disease conditions affecting the animals as well as human diseases putatively carried by the animals. It is important, therefore, to have well defined treatment, prophylactic and diagnostic procedures available to deal with infections or potential infections in animals and humans.

Pigs form a major component of the meat industry. However, pigs are sensitive to a wide spectrum of intestinal diseases collectively referred to as porcine proliferative enteropathy (PPE). This disease has previously been known as intestinal adentomatosis complex (1),

porcine intestinal adenomatosis (PIA), necrotic enteritis (2), proliferative haemorrhagic enteropathy (3), regional ileitis (4), haemorrhagic bowel syndrome (5), porcine proliferative enteritis and *Campylobacter* spp induced enteritis (6).

There are two main forms of PPE: a non-haemorrhagic form represented by intestinal adenomatosis which frequently causes growth retardation and mild diarrhoea; and a haemorrhagic form, which is often fatal, represented by proliferative haemorrhagic enteropathy (PHE) where the distal small intestine lumen becomes engorged with blood. PPE has been reported in a number of animal species including pigs (14), hamsters (7), ferrets (15), guinea pigs (16), rabbits (17) as well as avian species (18).

The causative organism of PPE is a *Campylobacter*-like organism referred to herein as *"Lawsonia intracellularis"* (26). The organism has also been previously referred to as *Ileal symbiont intracellularis* (7). PPE-like diseases in pigs may also be caused by other pathogens such as various species of *Campylobacter* (8).

Lawsonia intracellularis is an intracellular, possibly obligate intracellular, bacterium. It can only be cultured *in vitro* with tissue culture cells (9, 26). Pigs suffering from PPE are characterised by multiple abnormal immature crypts and *L. intracellularis* is located in the cytoplasm of these crypt cells.

PPE is a significant cost component associated with the pig industry, especially in terms of stock losses, medication costs, reduced growth rates of pigs and increased feed costs. PPE also contributes to downstream indirect costs in, for example, additional labour costs and environmental costs in dealing with antibiotic residue contamination and in control measures to prevent the organism being passed on or carried to other animals or humans.

Current control strategies for PPE rely on the use of antibiotics. However, such a strategy is considered to be short to medium term especially as governmental regulatory pressures tend to target animal husbandry practices which are only supported by prophylactic antibiotics. There

is a need, therefore, to develop effective, safe and low cost alternatives to the use of antibiotics. There is also a need to extend this alternative to antibiotics to similar organisms which infect other animals such as humans.

In work leading up to the present invention, the inventors sought to develop vaccines for the prophylaxis and treatment of PPE in animals and birds. The vaccines of the present invention provide an efficacious alternative to the use of antibiotics with a range of consequential husbandry and medical benefits.

Accordingly, one aspect of the present invention provides a vaccine composition for the prophylaxis or treatment of infection in an animal or bird by *L. intracellularis* or similar or otherwise related microorganism, said vaccine composition comprising an immunogenic, non-pathogenic form of *L. intracellularis* or related microorganism or an immunogenic component thereof and one or more carriers, diluents and/or adjuvants suitable for veterinary or pharmaceutical use.

The present invention is particularly useful and is exemplified hereinafter in relation to the protection and/or treatment of pigs from infection with *L. intracellularis*. However, this is done with the understanding that the present invention extends to the prophylaxis and treatment of all animals including humans and birds from infection with *L. intracellularis* and/or related microorganisms. Animals contemplated by the present invention include but are not limited to humans, primates, companion animals (e.g. cats, dogs), livestock animals (e.g. pigs, sheep, cattle, horses, donkeys, goats), laboratory test animals (e.g. mice, rats, guinea pigs, rabbits) and captive wild animals (e.g. kangaroos, foxes, deer). The present invention also extends to birds such as poultry birds, game birds and caged birds.

Furthermore, the present invention extends to all isolates and sub-types of *L. intracellularis* as well as other species of the genus *Lawsonia* or other microorganisms related thereto at the nucleotide, biochemical, structural, physiological and/or immunointeractive level. Reference hereinafter to *"Lawsonia intracellularis"* or its abbreviation *"L. intracellularis"* includes all

microorganisms similar to or otherwise related to this microorganism. For example, a related microorganism may have a nucleotide sequence similarity at the chromosome or extrachromosomal level of at least about 60%, more preferably at least about 70% and even more preferably greater than at least about 80% with respect to all or part of a nucleotide sequence within the chromosome or extrachromosomal elements of *L. intracellularis*. For example, these percentage similarities may relate to the sequence set forth in SEQ ID NO:5. This sequence is a portion of the *L. intracellularis* chromosome.

Accordingly, this aspect of the present invention is directed to a vaccine composition for the prophylaxis and/or treatment of infection in a pig by *L. intracellularis*, said vaccine composition comprising an immunogenic, non-pathogenic form of *L. intracellularis* or related microorganism or an immunogenic component thereof and one or more carriers, diluents and/or adjuvants suitable for veterinary or pharmaceutical use.

The term "immunogenic component" refers to *L. intracellularis* (in attenuated non-pathogenic or killed form) or a component of *L. intracellularis* including a peptide, polypeptide or a protein encoded by DNA from or derived from *L. intracellularis* which is capable of inducing a protective immune response in a pig. A protective immune response may be at the humoural and/or cellular level and generally results in a substantial reduction in the symptoms of PPE in pigs. The vaccine compositions will comprise an effective amount of immunogenic component such as to permit induction of a protective immune response.

According to this aspect of the present invention there is provided a vaccine composition for the prophylaxis and treatment of a pig by *L. intracellularis*, said vaccine composition comprising an amount of at least one immunogenic component from *L. intracellularis* or related microorganism effective to induce a protective immune response in said pig against *L. intracellularis* or related microorganism, said vaccine composition further comprising one or more carriers, adjuvants and/or diluents suitable for veterinary or pharmaceutical use.

The immunogenic component may be a naturally occurring peptide, polypeptide or protein, a

carbohydrate, lipid or nucleic acid (e.g. DNA) or any combination thereof isolated from *L. intracellularis* or a cell culture thereof or a recombinant form of a peptide, polypeptide or protein encoded by DNA from or derived from *L. intracellularis* or is a derivative of said peptide, polypeptide or protein.

An isolated component of *L. intracellularis* is a component which has undergone at least one purification step or which has undergone at least partial concentration from a cell culture comprising *L. intracellularis* or from a lysed preparation of *L. intracellularis* cells. The purity of such a component from *L. intracellularis* which has the requisite immunogenic properties is preferably at least about 40%, more preferably at least about 50%, even more preferably at least about 60%, still more preferably at least about 70% and even more preferably at least about 80-90% or greater relative to other components in a preparation as determined by molecular weight, immunogenic activity or other suitable means.

A particularly useful form of the vaccine is a whole cell vaccine which comprises *L. intracellularis* in attenuated or otherwise non-pathogenic form or killed cells or various fractions thereof.

Attenuated or non-pathogenic cells include killed *L. intracellularis* cells prepared, for example, by heat, formalin or other chemical treatment, electric shock or pressure and such cells are particularly useful in the practice of the present invention.

According to this aspect of the present invention there is provided a vaccine composition for the prophylaxis and/or treatment of infection in a pig by *L. intracellularis* or related microorganism said vaccine composition comprising a killed preparation of *L. intracellularis* or related microorganism or an immunogenic fraction thereof and one or more carriers, diluents and/or adjuvants suitable for veterinary or pharmaceutical use.

In an alternative embodiment, a recombinant vaccine may be employed. The recombinant vaccine may comprise one or more recombinant peptides, polypeptides or proteins derived from

L. intracellularis or is a recombinant molecule immunologically related to a peptide, polypeptide or protein derived from *L. intracellularis* or may be a fusion molecule having a first portion comprising a peptide, polypeptide or protein derived from *L. intracellularis* and a second heterologous peptide, polypeptide or protein which may be useful, for example, as a carrier molecule or an adjuvant or an immune stimulating molecule such as cytokine. A particularly useful recombinant protein from *L. intracellularis* comprises a peptide, polypeptide or protein derived from the cell surface or membrane of *L. intracellularis*, is an enzyme in a metabolic pathway within *L. intracellularis* or is a refolding and/or heatshock protein. In a preferred embodiment, the protein is a refolding/heatshock protein such as but not limited to GroEL and GroES. Other putative vaccine candidates include flagellar basal body rod protein, S-adenosylmethionine: tRNA ribosyltransferase-isomerase, enoyl-(acyl-carrier-protein) reductase, N-acetyl muramoyl-L-alanine amidase (autolysin), UOP-3-0-[3-hydroxymyristoyl] glucosamine N-acetyltransferase and a glucarate transporter.

According to a preferred embodiment, the present invention relates to a vaccine composition for the prophylaxis and/or treatment of infection in a pig by *L. intracellularis* or related microorganism, said vaccine composition comprising at least one recombinant peptide, polypeptide or protein from *L. intracellularis* and wherein said recombinant peptide, polypeptide or protein is capable of inducing a protective immune response against *L. intracellularis* in pigs, the vaccine composition further comprising one or more carriers, diluents and/or adjuvants suitable for veterinary or pharmaceutical use.

In a particularly preferred embodiment, the recombinant protein is GroEL having an amino acid sequence as set forth in SEQ ID NO:2 or is a protein having a predicted amino acid sequence with at least about 40%, at least about 60%, or more preferably at least about 70% and even more preferably at least about 80-90% or greater similarity to all or part of the amino acid sequence set forth in SEQ ID NO:2.

In another embodiment, the recombinant molecule is GroES having an amino acid sequence as set forth in SEQ ID NO:4 or is a molecule having an amino acid sequence at least about 40%,

at least about 60%, more preferably at least about 70% and even more preferably at least about 80-90% or greater similarity to all or part of the amino acid sequence set forth in SEQ ID NO:4.

Another embodiment of the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:1 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:3 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:5 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:6 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:8 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and

which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:11 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:13 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:15 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:17 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:18 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and

which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:19 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:20 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:21 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:22 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

In a related embodiment, the present invention includes and comprises a peptide, polypeptide or protein encoded by a nucleotide sequence as set forth in SEQ ID NO:23 or having at least 40% similarity thereto or capable of hybridizing thereto under low stringency conditions and

which nucleotide sequence encodes an immunogenic component of *L. intracellularis* or related microorganism.

Preferred percentage similarities include at least about 50% or at least about 60% or at least about 70-90%.

Reference herein to a low stringency at 42°C includes and encompasses from at least about 1% v/v to at least about 15% v/v formamide and from at least about 1M to at least about 2M salt for hybridisation, and at least about 1M to at least about 2M salt for washing conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions.

The present invention also contemplates peptides, polypeptides or proteins having an amino acid sequence substantially as set forth in one of SEQ ID NO:7 or 9 or 10 or 12 or 14 or 16 or having at least 40% similarity thereof or to all or part thereof. Preferred percentage similarities include at least about 50%, or at least about 60% or at least about 70-90%.

The present invention further extends to a vaccine comprising a recombinant vaccine vector encoding a peptide, polypeptide or protein derived from *L. intracellularis* or related microorganism as described above. The vaccine vector may be of viral, yeast or bacterial origin and would be capable of expression of a genetic sequence encoding a peptide, polypeptide or protein from *L. intracellularis* in a manner effective to induce a protective immune response. For example, a non-pathogenic bacterium could be prepared containing a recombinant sequence capable of encoding a peptide, polypeptide or protein from *L. intracellularis*. The recombinant sequence would be in the form of an expression vector under the control of a constitutive or

inducible promoter. The bacterium would then be permitted to colonise suitable locations in a pig's gut and would be permitted to grow and produce the recombinant peptide, polypeptide or protein in amount sufficient to induce a protective immune response against *L. intracellularis*.

In a further alternative embodiment, the vaccine may be a DNA vaccine comprising a DNA molecule encoding a peptide, polypeptide or protein from *L. intracellularis* and which is injected into muscular tissue or other suitable tissue in a pig under conditions sufficient to permit transient expression of said DNA to produce an amount of peptide, polypeptide or protein effective to induce a protective immune response.

The vaccines of the present invention may contain a single peptide, polypeptide or protein or a range of peptides, polypeptides or proteins covering different or similar epitopes. In addition, or alternatively, a single polypeptide may be provided with multiple epitopes. The latter type of vaccine is referred to as a polyvalent vaccine. A multiple epitope includes two or more repeating epitopes.

The formation of vaccines is generally known in the art and reference can conveniently be made to Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Co., Easton, Pennsylvania, USA.

The present invention, therefore, contemplates a pharmaceutical composition or vaccine composition comprising an immunity developing effective amount of one or more of:

(i) an immunogenic component from *L. intracellularis*;

(ii) a recombinant peptide, polypeptide or protein from *L. intracellularis* having immunogenic properties; and/or

(iii) whole cells or a component or fraction thereof from *L. intracellularis*.

The above components are referred to hereinafter as "active ingredients". The active

ingredients of a vaccine composition as contemplated herein exhibit excellent therapeutic activity, for example, in the treatment and/or prophylaxis of PPE when administered in an amount which depends on the particular case. For example, for recombinant molecules, from about 0.5 μg to about 20 mg may be administered. Other useful effective amounts include 1 μg to about 10 mg, 10 μg to about 5 mg and 50 μg to about 1 mg. The important feature is to administer sufficient to induce an effective protective immune response. The above amounts may be administered as stated or may be calculated per kilogram of body weight. Dosage regime may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. Booster administration may also be required.

The active ingredients may be administered in a convenient manner such as by the oral, intravenous (where water soluble), intramuscular, subcutaneous, intranasal, intradermal or suppository routes or implanting (eg using slow release technology). Depending on the route of administration, the active ingredients which comprise, for example, peptides, polypeptides or proteins may be required to be coated in a material to protect said ingredients from the action of enzymes, acids and other natural conditions which may inactivate said ingredients.

The term "adjuvant" is used in its broadest sense and includes any immune stimulating compound such as interferon. Adjuvants contemplated herein include resorcinols, non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecyl polyethylene ether and Freund's complete and incomplete adjuvant.

The active compounds may also be administered parenterally or intraperitoneally. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile

injectable solutions or dispersion. In all cases the form must be fluid to the extent that easy syringability exists unless the pharmaceutical form is a solid or semi-solid such as when slow release technology is employed. In any event, it must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms.

The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as licithin, by the maintenance of the required particle size in the case of dispersion and by the use of superfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

Carriers and diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents in vaccines is well known in the art. Except insofar as any conventional media or

agent is incompatible with an active ingredient, use thereof in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

Still another aspect of the present invention is directed to antibodies to the peptides, polypeptides or proteins from *L. intracellularis* or recombinant forms thereof or non-proteinaceous molecules such as carbohydrates. Such antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to *L. intracellularis* or may be specifically raised to specific molecules or whole cells or components or fractions thereof. The antibodies of the present invention are particularly useful for immunotherapy and vaccination and may also be used as a diagnostic tool for infection or for monitoring the progress of a vaccination or therapeutic regime.

For example, recombinant *L. intracellularis* peptides, polypeptides or proteins can be used to screen for naturally occurring antibodies to *L. intracellularis*. Alternatively, specific antibodies can be used to screen for *L. intracellularis*. Techniques for such assays are well known in the art and include, for example, sandwich assays and ELISA. Hereinafter, an immunogenic component is considered to encompass an immunogenic component of *L intracellularis* and includes recombinant molecules, whole cells and cell extracts.

In accordance with this aspect of the present invention, the immunogenic components are particularly useful in screening for antibodies to *L. intracellularis* and, hence, provide a diagnostic protocol for detecting *L. intracellularis* infection. Alternatively, biological samples can be directly screened for *L. intracellularis* using antibodies raised to immunogenic components.

Accordingly, there is provided a method for the diagnosis of *L. intracellularis* infection in a pig comprising contacting a biological sample from said pig with an immunogenic component binding effective amount of an antibody for a time and under conditions sufficient for an immunogenic component-antibody complex to form, and then detecting said complex.

The presence of immunogenic components (or antibodies thereto) in a pig's blood, serum, or other bodily fluid, can be detected using a wide range of immunoassay techniques such as those described in US Patent Nos. 4,016,043, 4,424,279 and 4,018,653. This includes both single-site and two-site, or "sandwich", assays of the non-competitive types, as well as in the traditional competitive binding assays. Sandwich assays are among the most useful and commonly used assays and are favoured for use in the present invention. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention.

Briefly, in a typical forward assay, an immunogenic component-specific antibody is immobilised onto a solid substrate to form a first complex and the sample to be tested for immunogenic component brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-immunogenic component secondary complex, a second immunogenic component antibody, labelled with a reporter molecule capable of producing a detectable signal, is then added and incubated, allowing sufficient time for the formation of a tertiary complex. Any unreacted material is washed away, and the presence of bound labelled antibody is determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal or may be quantitated by comparing with a control sample. The present invention contemplates a range of variations to the subject assay including an assay for *L. intracellularis* antibodies using, for example, recombinant peptides, polypeptides or proteins from this organism.

The solid substrate is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs or microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing the molecule to the insoluble carrier.

By "reporter molecule", as used in the present specification, is meant a molecule which, by its chemical nature, produces an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or quantitative. The most commonly used reporter molecule in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (i.e. radioisotopes). In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognised, however, a wide variety of different conjugation techniques exist which are readily available to one skilled in the art. Commonly used enzymes include horseradish peroxidase, glucose oxidase, β-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable colour change. It is also possible to employ fluorogenic substrates, which yield a fluorescent product.

Alternatively, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labelled antibody adsorbs the light energy, inducing a state of excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-hapten complex. After washing off the unbound reagent, the remaining ternary complex is then exposed to the light of the appropriate wavelength, the fluorescence observed indicates the presence of the hapten of interest. Immunofluorescence and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed. It will be readily apparent to the skilled technician how to vary the procedure to suit the required purpose.

A range of genetic diagnostic assays may be employed such as polymerase chain reaction (PCR) assays, hybridisation assays or protein truncation assays. All such assays are contemplated in the present invention.

The present invention is further described by the following non-limiting Figures and/or Examples.

In the Figures:

Figure 1 is a photographic representation showing Western analysis of *L. intracellularis* antigens recognised by vaccinated pigs. Track 1 (395) was probed with pig sera from a pig (395) that had been immunised three times with the formalin killed whole *L. intracellularis* vaccine. Track 2 to 5 (Y10, Y12, Y14, Y16) were probed with sera obtained from pigs Y10, Y12, Y14 and Y16, respectively on day 0.

Figure 2 is a photographic representation of the small intestine obtained from pig Y1 on day 20.

Figure 3 is a photographic representation of the small intestine obtained from pig Y2 on day 20.

Figure 4 is a photographic representation of the small intestine obtained from pig Y4 on day 20.

The following single and three letter abbreviations are used for amino acid residues:

Amino Acid	Three-letter Abbreviation	One-letter Symbol
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V
Any residue	Xaa	X

SUMMARY OF THE SEQUENCE IDENTITY NUMBERS

SEQ ID NO.	Description
1	Nucleotide sequence of GroEL
2	Amino acid sequence of GroEL
3	Nucleotide sequence of GroES
4	Amino acid sequence of GroES
5	Nucleotide sequence of *L. intracellularis* component
6	Nucleotide sequence of *L. intracellularis* component
7	Amino acid sequence of SEQ ID NO:6
8	Nucleotide sequence of *L. intracellularis* component
9	Amino acid sequence of SEQ ID NO:8 (first coding sequence)
10	Amino acid sequence of SEQ ID NO:8 (second coding sequence)
11	Nucleotide sequence of *L. intracellularis* component
12	Amino acid sequence of SEQ ID NO:11
13	Nucleotide sequence of *L. intracellularis* component
14	Amino acid sequence of SEQ ID NO:13
15	Nucleotide sequence of *L. intracellularis* component
16	Amino acid sequence of SEQ ID NO:15
17	Nucleotide sequence of *L. intracellularis* component
18	Nucleotide sequence of *L. intracellularis* component
19	Nucleotide sequence of *L. intracellularis* component
20	Nucleotide sequence of *L. intracellularis* component
21	Nucleotide sequence of *L. intracellularis* component
22	Nucleotide sequence of *L. intracellularis* component
23	Nucleotide sequence of *L. intracellularis* component

EXAMPLE 1

SOURCES OF PIG TISSUE

Infected Pig Intestines

Sections of grossly thickened ilea were taken from pigs naturally or experimentally affected by PPE. The presence of *L. intracellularis* bacteria in the ilea was confirmed using immunofluorescent staining with specific monoclonal antibodies (10). An example of a suitable antibody is monoclonal antibody IG4 available from the University of Edinburgh, UK.

EXAMPLE 2

ISOLATION OF *LAWSONIA INTRACELLULARIS* BACTERIA FROM THE INFECTED PIG ILEUM

Lawsonia intracellularis bacteria were extracted directly from lesions of PPE in pigs by filtration and further purified over a Percoll (Pharmacia, Uppsala, Sweden) gradient. Infected ilea were collected from pigs and the presence of *L. intracellularis* was confirmed histologically before storage at -80°C. Sections of ileum were thawed and approximately 8g of infected mucosa were scraped from the intestinal wall. The mucosa was homogenised with 40 ml sterile phosphate buffered saline (PBS) on half speed for 10 s using a Sorvall omnimixer. This suspension was centrifuged at 2000 *xg* for 4 minutes. The supernatant was discarded and the cell pellet was resuspended in 40 ml PBS and recentrifuged. This washing step was repeated twice. The cell pellet was then resuspended in 20 ml PBS and homogenised at full speed for one minute to release *L. intracellularis* bacteria.

This homogenate was centrifuged at 1000 *xg* for 4 minutes giving a pellet containing a crude mixture of homogenised epithelial cells and intestinal bacteria. The supernatant was filtered using filters with pore sized 3 μm, 1.2 μm and 0.8 μm (Millipore Corporation, MA, USA). The filtrate was centrifuged at 8000 *xg* for 30 minutes, resulting in a small pellet of *L. intracellularis* bacteria. The *L. intracellularis* bacteria were further purified using a 45% self forming percoll gradient as follows: 2 mls of the bacterial preparation was mixed by inversion into 30 mls of

a 45% self forming Percoll (Pharmacia LKB, Uppsala, Sweden) gradient (45% v/v of Percoll, 150 mM NaCl). The gradients were centrifuged in a Sorval centrifuge using the SS34 rotor, at 20,000rpm for 30 minutes at 4°C. Usually a number of bands form within the gradient. The band (usually located approx. 10-20mm from the base of the tube) containing the *L. intracellularis* bacteria was collected and the volume made up to 16 mls with PBS. The solution was then centrifuged for 15 minutes at 8000rpm. The resultant pellet was washed with PBS before being resuspended in a final volume of approximately one ml.

EXAMPLE 3

PURIFICATION OF *LAWSONIA INTRACELLULARIS* GENOMIC DNA

Genomic DNA was extracted from percoll-gradient purified *Lawsonia intracellularis* bacteria, recovered from infected pig ilea scrapings (Example 2), by the methods described by Anderson *et al* (11) & Sambrook *et al* (12).

EXAMPLE 4

IMMUNOSCREENING OF GENOMIC LIBRARIES

A lambda ZAP II *L. intracellularis* genomic library was plated on a lawn of *Escherichia coli* XLI-Blue (23) cells at a density of 2,000 plaque-forming units (pfu) per 150 mm L-broth agar plate. The library was screened with a rabbit anti- *L. intracellularis* sera using the method described in the Protoblot Technical Manual (Promega, WI, USA). Filters were blocked in a buffer containing 10mM Tris HCl, pH8.0, 150mM NaCl, 0.05% Tween 20, 1% w/w gelatin. Positive plaques identified in a primary screen were picked, replated at a lower density and rescreened until individual positive plaques were identified.

EXAMPLE 5

ISOLATION AND SEQUENCING OF cDNA INSERTS

Phagemid DNA from positive λZAP II phage clones was isolated by excision *in vivo* of the pBluescript phagemid under the conditions recommended by Stratagene (CA, USA). Plasmid

DNA was either extracted by the method of Birnboim and Doly and the cDNA inserts sequenced by the chain termination method (21), or by the PEG-precipitation method and cycle-sequenced by the dye-terminator method, as recommended by the manufacturer (Applied Biosystems).

EXAMPLE 6

ANTISERA

Antisera to *L. intracellularis* bacteria were raised in rabbits and pigs. Rabbits were injected intramuscularly with a preparation of Percoll gradient-purified *L. intracellularis* bacteria mixed with a double-emulsion made by processing with oil adjuvant (Freund's incomplete adjuvant, CSL Limited, Melbourne, Australia), and then with Tween 80 enhancer. Two 3 ml injections, containing 9 mg protein, were given four weeks apart. Blood samples were collected from the marginal ear vein prior to immunisation and two weeks following the second injection.

A 6-week old pig (395) was hyperimmunised by intramuscular injection of Percoll gradient purified *L. intracellularis* bacteria prepared with Freund's incomplete adjuvant as for the rabbit. Three injections of the prepared antigen were administered four weeks apart, and blood was collected from the jugular vein two weeks following the final injection. Diluted pig sera (1 ml, 1 in 200) were pre-absorbed with 100 μl *E. coli* DH5α (24) lysate for 1 h at room temperature with gentle mixing. The lysate was prepared by freeze-thawing a suspension of *E. coli* in PBS.

EXAMPLE 7

SODIUM DODECYL SULFATE-POLYACRYLAMIDE GEL ELECTROPHORESIS (SDS-PAGE)

Protein samples were resuspended in 50 μl of sample buffer (62.4 mM HCl, 2% w/v SDS, 10% v/v glycerol, 5% v/v 20 mercaptoethanol, 0.002% bromophenol blue, pH 6.8) and heated to 95°C for 5 minutes before separating solubilised proteins electrophoretically on a 0.1% w/v SDS-12% w/v PAGE vertical slab gel (13).

EXAMPLE 8

WESTERN BLOTTING

Proteins were electrophoretically transferred to Immobilon-P (Millipore Corporation, MA, USA) membranes in a Trans-Blot Cell (BioRad, CA, USA) at 100 V for 1 h in a buffer containing CAPS (3-[Cyclohexylamino]-l-propanesulfonic acid, pH 11, Sigma, MI, USA) and 10% v/v methanol. The membranes were then blocked with 5% w/v Blotto (Diploma skim milk powder, Melbourne, Australia) in PBS for 30 min at room temperature with gentle rocking. The filters were then transferred to antisera diluted in 5% w/v Blotto, PBS. Pre-absorbed pig antisera was diluted 1 in 200. The filters were incubated in pig antisera for 1 h followed by washing three times in PBST.

HRP conjugated anti-swine immunoglobulins (DAKO, CA, USA) were applied at a dilution of 1:2000. Enhanced Chemiluminescence (ECL, Amersham, IL, USA) was used to discriminate *L. intracellularis* proteins. Prior to ECL detection, blots were washed three times for 7 minutes each. The filters were exposed to autoradiographic film (Agfa, NJ, USA) for less than 1 minute before developing.

EXAMPLE 9

IDENTIFICATION OF GroEL AND GroES

Clones found to be positive according to the immunoscreening method described in Example 4 were sequenced using the protocol detailed in Example 5. One clone isolated represented the GroEL protein. The nucleotide sequence and corresponding amino acid sequence of GroEL are shown in SEQ ID NO:1 and SEQ ID NO:2. Another clone isolated represented the GroES protein. The nucleotide sequence of GroES and corresponding amino acid sequence are shown in SEQ ID NO:3 and SEQ ID NO:4.

EXAMPLE 10

IMMUNOFLORESCENT DETECTION OF *LAWSONIA INTRACELLULARIS* BACTERIA IN PIG FAECES

Faecal swabs of pigs were taken using a cotton tipped swab and then the sample was smeared onto a glass slide. After allowing ten minutes for air drying the smears were heat fixed by heating to 60°C for approximately 10 seconds. The slides were then rinsed in PBS. An amount of 30μl of a 1/200 dilution of a mouse ascites containing IG4 monoclonal antibody (see Example 1) was added, a glass cover slip applied, and the slides were incubated at room temperature for 40 minutes. The cover slip was removed and the slides were washed (PBST for 7 minutes, three times). An amount of 30μl of a 1/40 dilution of a FITC conjugated anti-mouse antiserum (Silenus, Melbourne Australia) was added, a glass cover slip applied and the slides were incubated at room temperature for 40 minutes. The cover slip was removed and the slides were washed (PBST for 7 minutes X3). The slides were given a final rinse in PBS. A drop of 10% v/v glycerol PBS was added and a glass cover slip applied. The fluorescent bacteria were visualised under highpower (X1200) at 340 nm using a Lietz laborlux S microscope. Twenty fields were counted and the results (see Table 1) were expressed as the average number of *L. intracellularis* bacteria per high powered field.

EXAMPLE 11

FORMALIN-KILLED *L. INTRACELLULARIS* VACCINE

The percoll gradient purified bacterial *L. intracellularis* pellet was resuspended in 1 ml of 1% formalin in saline and incubated overnight at 4°C. The percoll gradient-purified *L. intracellularis* bacteria was then mixed into a double-emulsion made by processing with oil adjuvant (Freund's incomplete adjuvant, Commonwealth Serum Laboratories, Melbourne, Australia), and then with Tween 80 enhancer.

EXAMPLE 12

VACCINATION PROTOCOL

Twelve weaned pigs (Landrace crossed with Large White) were sourced from a Pig Improvement Company piggery and treated with Neo- Terramycin (0.25 g/kilo) for 5 days. Seven days later (day -40) pigs Y10, Y12, Y14 and Y16 were vaccinated as described. Pigs Y3, Y11 and Y13 were treated for abscess with long acting terramycin on day -34.

The twelve pigs were divided into three groups and treated as follows:

Group 1 Infected Controls

Four pigs (Ear Tag No Y1-Y4) were housed with vaccinated pigs.

Group 2 Whole Bacteria Vaccine

Four pigs (Ear Tag No. Y10, Y12, Y14 and Y16) were immunised with 0.5 ml formalin killed *L. intracellularis* bacteria emulisifed in 0.5 ml of PBS/Freunds incomplete adjuvant on days -33 and -12.

Group 3 Uninfected Controls

Four pigs (Ear Tag No. Y9, Y11, Y13 and Y15) received no treatments and were housed in a separate area from the vaccinated pigs and infected control pigs.

EXAMPLE 13

ORAL CHALLENGES OF INFECTED PIGS

Infected ilea were collected from pigs as described in Example 1 and the presence of *L. intracellularis* was confirmed histologically before storage at -80°C. Sections of ileum were thawed and approximately 150g of infected mucosa was scraped from the intestinal wall. The mucosa was homogenised with an equal volume of sterile PBS on half speed for 20 s using a

Sorvall ominimixer. This suspension was diluted two fold with sterile PBS to form the challenge suspension.

On day 0 each pig from Groups 1 and 2 was dosed with a 5% w/v with Na Bicarbonate solution (10 ml/kg) followed by 30 ml of the challenge suspension. This was repeated on day 1 and day 2.

From day 11 onwards, the number of *L. intracellularis* bacteria in each pig's faeces was monitored by immunoflorescence. Pigs were monitored for signs of disease and shedding of *L intracellularis* bacteria. Pigs shedding greater than 100 bacteria per high powered field and scouring were killed for ethical reasons.

On day 22 the surviving pigs were humanely killed and the small intestines were recovered. Two sections of small intestine were removed 5 cms and 17 cms proximally from the ileocaecal junction. These sections were fixed in 10% v/v formalin, wax embedded and sections were sent to an independent veterinary pathologist for analysis.

EXAMPLE 14

LAWSONIA INTRACELLULARIS PROTEINS RECOGNISED BY VACCINATED PIGS

Antibodies raised by pigs to *L. intracellularis* proteins post vaccination were analysed by Western blotting followed by ECL (Amersham, IL, USA) detection as described in Example 8. The results are shown in Figure 1. Vaccinated pigs produce antibodies to a range *of L. intracellularis* proteins. The most immunodominant proteins recognised are approximately 62.7 Kda, 58.7 Kda, 57.2 Kda, 44 Kda, 36.7 Kda and two smears from 24-26 Kda and 22-23.5 Kda. Minor immunoreactive bands had approximately the following molecular weights 67 Kda, 52.5 Kda, 50.5 Kda, 50 Kda, 48.2 KDa, 47.9 Kda, 44.7 Kda, 43.5 Kda, 42.5 Kda, 41.5 Kda, 40.5 Kda, 39 Kda, 35.3 Kda, 17 Kda, 15.5 Kda, 12 Kda and 7 Kda. The molecular weight of the proteins recognised will vary by up to 5% depending on the method used for estimation.

EXAMPLE 15

SHEDDING OF *L. INTRACELLULARIS* BACTERIA BY PIGS DURING TRIAL

Three of the pigs from Group 1 (Infected control) in Example No. 12 (Y1, Y2 and Y4) shed greater than 100 *L. intracellularis* bacteria per high powered field in their faeces by day 19 post oral challenge (Table 1). Two of these pig (Y2 and Y4) had a bloody scour. All three pigs were humanely killed on day 20. Y3 shed low levels of *L. intracellularis* bacteria during the course of the infection trial. Maximal bacterial shedding for Y3 was 16 bacteria per high powered field.

All pigs in group 3 vaccinated with whole bacteria as set out in Example 12, never shed more than 3 *L. intracellularis* bacteria per high powered field. Vaccination with the formalin killed *L. intracellularis* vaccine reduced total bacterial shedding of *L. intracellularis* bacteria by vaccinated pigs by 98.5% when compared with group 1 pigs.

None of the group 3 pigs (uninfected controls) shed any *L. intracellularis* bacteria during the course of the trial.

The results of shedding of *L. intracellularis* bacteria per pig are shown in Table 1.

EXAMPLE 16

GROSS PATHOLOGY FOR TRIAL A

Group 1 *Infected Controls*

Y1 Approximately 5 cm of terminal ileum was grossly thickened. No other signs of PPE were evident macroscopically. Findings are consist with intestinal adenomatosis (See Figure 2).

Y2 The intestine was found to be grossly thickened and the serosa had the characteristic cerebriform forms (Figure 3). Over 2.5 metres of the intestine was involved. The lumen of the intestine was found to contain fresh blood and fibrinous casts were evident.

Proliferative haemorrhagic enteropathy.

Y3 No gross signs of PPE were evident.

Y4 The intestine was found to have necrotic enteritis (Figure 4). The mucosal surface was replaced with a fibrinous pseudomembrane. Oedema of the mesentery was clearly evident. Over 2.0 meters of intestine was involved.

Group 2 *Whole L. intracellularis cell vaccine*

Y10 No gross signs of PPE.

Y12 No gross signs of PPE.

Y14 No gross signs of PPE.

Y16 No gross signs of PPE.

Group 3 *Uninfected controls*

Y9 No gross signs of PPE.

Y11 No gross signs of PPE.

Y13 No gross signs of PPE.

Y15 No gross signs of PPE.

EXAMPLE 17

HISTOPATHOLOGY REPORT FOR TRIAL

Reports are based on established histopathological descriptions in Jubb *et al* (20).

Group 1 *Infected control group*

Y1 Numerous microfocal/confluent lesions of Porcine Intestinal Adenomatosis (PIA) are associated with Peyers Patches.

Y2 Serious generalised (annular) lesions of Porcine Intestinal Adenomatosis.

Y3 No conclusive evidence of PIA. Sparse microfocal lesions suggestive of a non-specific mild reactive (reparational) hyperplasia (rather than an adenomatosis).

Y4 Severe generalised (annular) lesions of PIA.

Group 2 *Whole L. intracellularis cell vaccine*

Y10 No conclusive evidence of PIA.

Y12 No conclusive evidence of PIA.

Y14 No conclusive evidence of PIA.

Y16 No conclusive evidence of PIA. Possible single microfocus of PIA is associated with Peyers Patch.

Group 3 *Uninfected controls*

Y11 No conclusive evidence of PIA.

Y9 No conclusive evidence of PIA.

Y13 Intestine was not recovered since pig was killed due to lameness at day 15.

Y15 Diagnosis not possible because of the poor quality sections.

EXAMPLE 18

IMMUNOSCREENING OF A *L. INTRACELLULARIS* LIBRARY USING EXPERIMENTAL SERA FROM VACCINATED PIGS

L. intracellularis genomic DNA was purified as described in Example 3. The DNA was partially digested with the restriction endonuclease *Sau*3A (Promega) and ligated into Lambda ZAP II Express (Stratagene). The lambda library was plated on a lawn of *E. coli* XLI-Blue cells at a density of 10,000 pfu per 150 Mm L-broth agar plate. The library was screened, as described in Example 4, with sera from Y12. The pig Y12 was immunised with formalin killed *L. intracellularis*, as described in Example 11 & 12. Vaccinated pigs produced antibodies to a range of *L. intracellularis* proteins, as described in Example 14. A number of phage clones expressing *L. intracellularis* proteins were identified.

EXAMPLE 19

ANALYSIS OF *L. INTRACELLULARIS* EXPRESSING PHAGE CLONES

Phagemid DNA from positive λZAP II Express phage clones was isolated by *in vivo* excision, by the conditions recommended by the manufacturer (Stratagene). Plasmid DNA, for restriction analysis was extracted by alkaline-lysis, as described by Sambrook *et al* (12), and for automated sequencing, using the High Pure Plasmid Kit, as recommended by the manufacturer (Boehringer Mannheim). DNA sequencing of inserts was performed by the Dye-terminator method of automated sequencing (ABI Biosystems). The sequences identified are set out in SEQ ID NOS: 5-23 (see Example 20).

EXAMPLE 20

IDENTIFICATION OF *L. INTRACELLULARIS* COMPONENTS

Sequence similarity of the DNA molecules encoding putative vaccine candidates identified from Example 18 and 19, was identified using BLAST (27). Nucleotide sequence SEQ ID NO:6 and its corresponding amino acid sequence SEQ ID NO:7 have sequence similarity to flagellar basal body rod protein. SEQ ID NO:8 (nucleotide) and SEQ ID NOS:9 and 10 (amino acid) have sequence similarity to autolysin. SEQ ID NO:11 (nucleotide) and SEQ ID NO:12 (amino acid) show sequence similarity to S-adenosylmethionine: tRNA ribosyltransferase-isomerase (queuosine biosynthesis protein queA).

SEQ ID NO:13 (nucleotide) and SEQ ID NO:14 (amino acid) show sequence similarity to enoyl-(acyl-carrier-protein) reductase. SEQ ID NO:15 (nucleotide) and SEQ ID NO:16 (amino acid) show sequence similarity to a glucarate transporter. Other nucleotide sequences encoding putative vaccine candidates are SEQ ID NO:5, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22 and SEQ ID NO:23.

Those skilled in the art will appreciate that the invention described herein is susceptible to

variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

TABLE 1

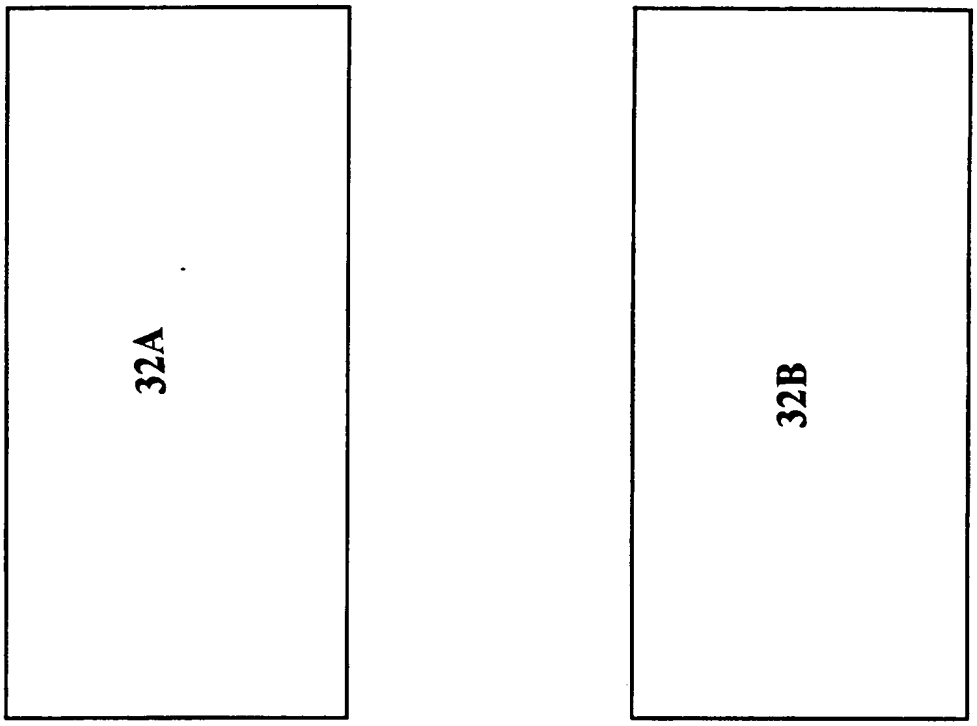

TABLE 1

	Vaccination			Challenge															
	Day -40	Day -33	Day -26	Day -12	Day 0	Day 1	Day 2	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22
1 infected controls								1+	1+	0	0	5+	10+	50+	100+	15	5 cm of thickening		
2 infected controls								0	1+	1+	1+	3+	1+	70+	100+	100	PHE 2.5 M		
3 infected controls								0	0	0	0	0	0	1+	4	16	1+	0	1
4 infected controls								1+	0	0	10+	0	5+	60+	200+	80	PHE 2.0 M		
10 whole bugs		1 ml killed whole cell		1 ml killed whole cell				0	0	0	0	0	1+	1+	0	0	0	0	0

12 whole bugs	1 ml killed whole cell 1 ml killed whole cell	1+	0	0	0	0	2+	0	0	0	0	0	0
14 whole bugs	1 ml killed whole cell 1 ml killed whole cell	0	0	0	0	0	1+	0	<1	<1	0	0	0
16 whole bugs	1 ml killed whole cell 1 ml killed whole cell	0	0	0	0	0	0	0	3	<1	0	0	0
9 Uninfected controls		0	0	0	0	0	0	0	0	0	0	0	0
11 Uninfected controls		0	0	0	0	0	0	0	0	0	0	0	0
13 Uninfected controls		0	0	0	0	Killed Lane							
15 Uninfected controls		0	0	0	0	0	0	0	0	0	0	0	0

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: (OTHER THAN US) DARATECH PTY LTD and PIG RESEARCH
(US ONLY): MICHAEL PANACCIO and DETLEF HASSE

(ii) TITLE OF INVENTION: THERAPEUTIC AND DIAGNOSTIC COMPOSITIONS

(iii) NUMBER OF SEQUENCES: 23

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(v) COMPUTER READABLE FORM:
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(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
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(A) APPLICATION NUMBER: PN6910/95

(B) FILING DATE: 30-NOV-1995

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1647 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..1647

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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ATG GCT TCT AAA GAA ATC CTT TTT GAT GCT AAA GCC CGT GAA AAA CTT      48
Met Ala Ser Lys Glu Ile Leu Phe Asp Ala Lys Ala Arg Glu Lys Leu
 1               5                  10                  15

TCA CGA GGT GTA GAT AAA CTT GCA AAT GCT GTT AAA GTA ACA CTT GGA      96
Ser Arg Gly Val Asp Lys Leu Ala Asn Ala Val Lys Val Thr Leu Gly
            20                  25                  30

CCT AAA GGC CGT AAT GTC GTT ATT GAA AAG TCT TTT GGT TCC CCA GTT     144
Pro Lys Gly Arg Asn Val Val Ile Glu Lys Ser Phe Gly Ser Pro Val
        35                  40                  45

ATT ACA AAA GAT GGT GTA TCT GTT GCA AAA GAA ATT GAA CTT GAA GAT     192
Ile Thr Lys Asp Gly Val Ser Val Ala Lys Glu Ile Glu Leu Glu Asp
    50                  55                  60

AAG TTT GAA AAT ATG GGC GCT CAA ATG GTT AAA GAA GTA GCT CCC AAA     240
Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu Val Ala Pro Lys
65                  70                  75                  80
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ACT AGC GAT ATT GCT GGT GAT GGA ACT ACA ACA GCA ACA GTC CTT GCA      288
Thr Ser Asp Ile Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala
                85                  90                  95

CAA GCT ATT TAT CGT GAA GGT GTA AAA CTT GTA GCA GCT GGT CGT AAT      336
Gln Ala Ile Tyr Arg Glu Gly Val Lys Leu Val Ala Ala Gly Arg Asn
            100                 105                 110

CCT ATG GCC ATT AAA CGT GGC ATA GAT AAA GCT GTT GTT GCT GTT ACT      384
Pro Met Ala Ile Lys Arg Gly Ile Asp Lys Ala Val Val Ala Val Thr
        115                 120                 125

AAA GAA CTA AGC GAC ATT ACA AAG CCT ACT CGT GAC CAA AAA GAA ATA      432
Lys Glu Leu Ser Asp Ile Thr Lys Pro Thr Arg Asp Gln Lys Glu Ile
    130                 135                 140

GCT CAA GTT GGA ACC ATT TCT GCA AAC TCT GAT ACA ACA ATA GGT AAT      480
Ala Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Thr Thr Ile Gly Asn
145                 150                 155                 160

ATC ATA GCT GAA GCT ATG GCT AAA GTT GGA AAA GGA GGT GTT ATC ACA      528
Ile Ile Ala Glu Ala Met Ala Lys Val Gly Lys Gly Gly Val Ile Thr
                165                 170                 175

GTT GAG GAA GCT AAA GGT CTT GAA ACT ACA TTA GAT GTG GTT GAA GGA      576
Val Glu Glu Ala Lys Gly Leu Glu Thr Thr Leu Asp Val Val Glu Gly
            180                 185                 190

ATG AAG TTT GAC CGT GGC TAC CTC TCT CCA TAC TTT GTA ACT AAT CCT      624
Met Lys Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Val Thr Asn Pro
        195                 200                 205

GAG AAA ATG GTT TGT GAA CTT GAT AAC CCT TAT ATC CTT TGT AAT GAG      672
Glu Lys Met Val Cys Glu Leu Asp Asn Pro Tyr Ile Leu Cys Asn Glu
    210                 215                 220

AAA AAG ATT ACT AGC ATG AAA GAC ATG CTA CCA ATC TTA GAA CAA GTT      720
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Lys Lys Ile Thr Ser Met Lys Asp Met Leu Pro Ile Leu Glu Gln Val
225                 230                 235                 240

GCT AAA GTA AAC CGT CCA CTC CTT ATT ATT GCT GAA GAC GTA GAA GGT      768
Ala Lys Val Asn Arg Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly
                245                 250                 255

GAA GCA CTT GCA ACA CTT GTA GTC AAT AAG CTC CGT GGA GCA CTC CAA      816
Glu Ala Leu Ala Thr Leu Val Val Asn Lys Leu Arg Gly Ala Leu Gln
            260                 265                 270

GTT GTA GCC GTA AAA GCT CCT GGT TTT GGT GAA CGC CGT AAA GCT ATG      864
Val Val Ala Val Lys Ala Pro Gly Phe Gly Glu Arg Arg Lys Ala Met
        275                 280                 285

CTT GAA GAT ATT GCT ATC CTT ACT GGA GGA GAA GCA ATA TTT GAA GAT      912
Leu Glu Asp Ile Ala Ile Leu Thr Gly Gly Glu Ala Ile Phe Glu Asp
    290                 295                 300

CGT GGT ATA AAG CTT GAA AAT GTA AGC TTG TCT TCT TTA GGA ACA GCT      960
Arg Gly Ile Lys Leu Glu Asn Val Ser Leu Ser Ser Leu Gly Thr Ala
305                 310                 315                 320

AAA CGT GTA GTT ATT GAC AAA GAA AAT ACT ACT ATC GTT GAT GGT GCT     1008
Lys Arg Val Val Ile Asp Lys Glu Asn Thr Thr Ile Val Asp Gly Ala
                325                 330                 335

GGA AAA TCA GAA GAT ATT AAA GCT CGA GTT AAA CAA ATT CGT GCA CAA     1056
Gly Lys Ser Glu Asp Ile Lys Ala Arg Val Lys Gln Ile Arg Ala Gln
            340                 345                 350

ATT GAA GAA ACA AGC TCA GAT TAT GAT CGT GAA AAA CTT CAA GAA CGT     1104
Ile Glu Glu Thr Ser Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg
        355                 360                 365

CTT GCA AAA CTT GTT GGT GGA GTA GCT GTT ATC CAT GTT GGA GCT GCT     1152
Leu Ala Lys Leu Val Gly Gly Val Ala Val Ile His Val Gly Ala Ala
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    370                 375                 380

ACT GAA ACT GAA ATG AAA GAG AAG AAG GAT CGT GTA GAA GAT GCT CTA      1200
Thr Glu Thr Glu Met Lys Glu Lys Lys Asp Arg Val Glu Asp Ala Leu
385                 390                 395                 400

AAT GCA ACA AGA GCT GCG GTT GAA GAA GGT ATT GTC CCT GGT GGT GGT      1248
Asn Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly Gly
                405                 410                 415

ACT GCT TTT GTC CGC TCC ATT AAA GTC CTT GAT GAT ATT AAA CCT GCT      1296
Thr Ala Phe Val Arg Ser Ile Lys Val Leu Asp Asp Ile Lys Pro Ala
            420                 425                 430

GAT GAT GAT GAA CTT GCT GGA CTT AAT ATC ATC CGT CGT TCT CTT GAA      1344
Asp Asp Asp Glu Leu Ala Gly Leu Asn Ile Ile Arg Arg Ser Leu Glu
        435                 440                 445

GAG CCT TTA CGT CAA ATT GCT GCA AAT GCT GGC TAT GAA GGT TCT ATT      1392
Glu Pro Leu Arg Gln Ile Ala Ala Asn Ala Gly Tyr Glu Gly Ser Ile
    450                 455                 460

GTT GTA GAA AAA GTT CGT GAA CCA AAA GAT GGT TTT GGA TTT AAT GCT      1440
Val Val Glu Lys Val Arg Glu Pro Lys Asp Gly Phe Gly Phe Asn Ala
465                 470                 475                 480

GCA TCA GGA GAA TAT GAA GAC CTT ATT AAA GCT GGT GTC ATT GAT CCT      1488
Ala Ser Gly Glu Tyr Glu Asp Leu Ile Lys Ala Gly Val Ile Asp Pro
                485                 490                 495

AAA AAA GTT ACA CGT ATT GCA TTA CAA AAT GCA GCA TCA GTA GCC TCC      1536
Lys Lys Val Thr Arg Ile Ala Leu Gln Asn Ala Ala Ser Val Ala Ser
            500                 505                 510

TTA CTT CTA ACT ACA GAA TGC GCT ATT GCT GAA AAA CCA GAA CCT AAA      1584
Leu Leu Leu Thr Thr Glu Cys Ala Ile Ala Glu Lys Pro Glu Pro Lys
        515                 520                 525
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AAA GAT ATG CCT ATG CCT GGC GGT GGT ATG GGT GGT ATG GGT GGT ATG      1632
Lys Asp Met Pro Met Pro Gly Gly Gly Met Gly Gly Met Gly Gly Met
    530                 535                 540

GAC GGT ATG TAC TAG                                                 1647
Asp Gly Met Tyr
545
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 548 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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 1               5                  10                  15

Ser Arg Gly Val Asp Lys Leu Ala Asn Ala Val Lys Val Thr Leu Gly
            20                  25                  30

Pro Lys Gly Arg Asn Val Val Ile Glu Lys Ser Phe Gly Ser Pro Val
        35                  40                  45

Ile Thr Lys Asp Gly Val Ser Val Ala Lys Glu Ile Glu Leu Glu Asp
    50                  55                  60

Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu Val Ala Pro Lys
65                  70                  75                  80

Thr Ser Asp Ile Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala
                85                  90                  95
```

Gln Ala Ile Tyr Arg Glu Gly Val Lys Leu Val Ala Ala Gly Arg Asn
100 105 110

Pro Met Ala Ile Lys Arg Gly Ile Asp Lys Ala Val Val Ala Val Thr
115 120 125

Lys Glu Leu Ser Asp Ile Thr Lys Pro Thr Arg Asp Gln Lys Glu Ile
130 135 140

Ala Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Thr Thr Ile Gly Asn
145 150 155 160

Ile Ile Ala Glu Ala Met Ala Lys Val Gly Lys Gly Gly Val Ile Thr
165 170 175

Val Glu Glu Ala Lys Gly Leu Glu Thr Thr Leu Asp Val Val Glu Gly
180 185 190

Met Lys Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Val Thr Asn Pro
195 200 205

Glu Lys Met Val Cys Glu Leu Asp Asn Pro Tyr Ile Leu Cys Asn Glu
210 215 220

Lys Lys Ile Thr Ser Met Lys Asp Met Leu Pro Ile Leu Glu Gln Val
225 230 235 240

Ala Lys Val Asn Arg Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly
245 250 255

Glu Ala Leu Ala Thr Leu Val Val Asn Lys Leu Arg Gly Ala Leu Gln
260 265 270

Val Val Ala Val Lys Ala Pro Gly Phe Gly Glu Arg Arg Lys Ala Met
275 280 285

Leu Glu Asp Ile Ala Ile Leu Thr Gly Gly Glu Ala Ile Phe Glu Asp

290 295 300

Arg Gly Ile Lys Leu Glu Asn Val Ser Leu Ser Ser Leu Gly Thr Ala
305 310 315 320

Lys Arg Val Val Ile Asp Lys Glu Asn Thr Thr Ile Val Asp Gly Ala
325 330 335

Gly Lys Ser Glu Asp Ile Lys Ala Arg Val Lys Gln Ile Arg Ala Gln
340 345 350

Ile Glu Glu Thr Ser Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg
355 360 365

Leu Ala Lys Leu Val Gly Gly Val Ala Val Ile His Val Gly Ala Ala
370 375 380

Thr Glu Thr Glu Met Lys Glu Lys Lys Asp Arg Val Glu Asp Ala Leu
385 390 395 400

Asn Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly Gly
405 410 415

Thr Ala Phe Val Arg Ser Ile Lys Val Leu Asp Asp Ile Lys Pro Ala
420 425 430

Asp Asp Asp Glu Leu Ala Gly Leu Asn Ile Ile Arg Arg Ser Leu Glu
435 440 445

Glu Pro Leu Arg Gln Ile Ala Ala Asn Ala Gly Tyr Glu Gly Ser Ile
450 455 460

Val Val Glu Lys Val Arg Glu Pro Lys Asp Gly Phe Gly Phe Asn Ala
465 470 475 480

Ala Ser Gly Glu Tyr Glu Asp Leu Ile Lys Ala Gly Val Ile Asp Pro
485 490 495

Lys Lys Val Thr Arg Ile Ala Leu Gln Asn Ala Ala Ser Val Ala Ser
500 505 510

Leu Leu Leu Thr Thr Glu Cys Ala Ile Ala Glu Lys Pro Glu Pro Lys
515 520 525

Lys Asp Met Pro Met Pro Gly Gly Gly Met Gly Gly Met Gly Gly Met
530 535 540

Asp Gly Met Tyr
545

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 306 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..306

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATG AAC CTG AAA CCT TTG AAT GAC CGT GTT TTA GTA AAA CGT CTT GAA 48
Met Asn Leu Lys Pro Leu Asn Asp Arg Val Leu Val Lys Arg Leu Glu
1 5 10 15

TCT GAA GAA AAA ACA GCT GGT GGA CTC TAT ATC CCT GAT ACT GCT AAA 96
Ser Glu Glu Lys Thr Ala Gly Gly Leu Tyr Ile Pro Asp Thr Ala Lys
20 25 30

```
GAA AAA CCA TCT CGT GGT GAA GTT GTT GCT GTT GGA CCT GGT AAA CAT      144
Glu Lys Pro Ser Arg Gly Glu Val Val Ala Val Gly Pro Gly Lys His
          35                  40                  45

ACA GAT GAT GGT AAA TTA ATA CCT ATG GCT GTA AAA GCA GGA GAT ACA      192
Thr Asp Asp Gly Lys Leu Ile Pro Met Ala Val Lys Ala Gly Asp Thr
      50                  55                  60

GTT CTT TTT AAT AAG TAT GCA GGA ACA GAA GTA AAG CTT GAT GGT GTA      240
Val Leu Phe Asn Lys Tyr Ala Gly Thr Glu Val Lys Leu Asp Gly Val
 65                  70                  75                  80

GAG CAT CTA GTT ATG CGT GAA GAT GAC ATC CTA GCT GTT ATT ACT GGA      288
Glu His Leu Val Met Arg Glu Asp Asp Ile Leu Ala Val Ile Thr Gly
                 85                  90                  95

GAA ACT GGC CGC AAG TGA                                             306
Glu Thr Gly Arg Lys  *
            100
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 101 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Met Asn Leu Lys Pro Leu Asn Asp Arg Val Leu Val Lys Arg Leu Glu
 1               5                  10                  15

Ser Glu Glu Lys Thr Ala Gly Gly Leu Tyr Ile Pro Asp Thr Ala Lys
```

20 25 30

Glu Lys Pro Ser Arg Gly Glu Val Val Ala Val Gly Pro Gly Lys His
35 40 45

Thr Asp Asp Gly Lys Leu Ile Pro Met Ala Val Lys Ala Gly Asp Thr
50 55 60

Val Leu Phe Asn Lys Tyr Ala Gly Thr Glu Val Lys Leu Asp Gly Val
65 70 75 80

Glu His Leu Val Met Arg Glu Asp Asp Ile Leu Ala Val Ile Thr Gly
85 90 95

Glu Thr Gly Arg Lys
100

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4972 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

AACTCCTGGT CTATCAAGAT CAACTAAAAA ATATTCTTTA TCTAATAGTT 50
GCTCAAAAAT AATTGTACCT ACAGGTAAAT GAAGAATCAA ATCTTCCCCT 100
TTTTTACCAT GACGCTGGCT CCCTTTACCA CCTTCTCCAT TTTGAGCTCT 150
ATAGTGACGT TGCACACGAA AATCATAAAG GGTTAACAAA CGTGAATCAG 200
CTTTAAAAAT TATATTACCT CCATCTCCTC CATCCCCTCC ATTAGGTCCA 250

CCTTTAGGTA TAAACTTTTC GCGTCTAAAT GAAACACATC CATTTCCACC 300
TTTTCCTGCG CTCACGCTAA TAGTTACTTC ATCAACAAAA CGCATGATTA 350
TCCTTTCAAT AACAAATATC TATTCAATAC TGTTACTAAC TTGTTTACTG 400
TTTTTTCTAG AAAATTACCT GGCTAATTAT TATAGTTATA TCTAGATTAA 450
TGAAAAAGGA AGAAGTCATT ACACTCCTTC CTTATTAATA GAATCCTGGA 500
ATAATTATTA TACGGTGGGT TGTATATGCA CTCTACTATA TCTTTTACAT 550
TTACGAAAAT ATGTTTCATA AGTTACTATA CCATTAACTT TTGCAAATAA 600
AGTATAGTCT CTTCCCATTC CAACATTTTC TCCAGGATGA ATTTTTGTAC 650
CTAGTTGACG AACAAGGATA TTGCCTGCCA AGACTTTCTG GCCGCCGAAA 700
CGCTTTATAC CACGACGTTG TCCTGGACTA TCTCTACCAT TGCGAGAACT 750
TCCACCAGCT TTCTTATGGG CCATTTTAAT ATCTCCTTAA AGCTGAATAC 800
CTGTTACTTT TAGAGCTGTA TAGTCTTGAC GATGACCTTG GAGTTTACGT 850
GAGTCATTTC TTCTCCACTT TTTAAAAACA AGAATTTTTT TATCACGACC 900
ATGCTCAAGA ACTTTAGCTA TAACTTTAGC ATTATTAATA TATGGTGTTC 950
CAATTTGAGG AGATGAACCA CCAATCATAA AAATTTTATC AAAAAAAATT 1000
TCTGTTCCAA CTTCAGCGTC TATTTTAGAA ACAAAAATTT TAGAACCCTC 1050
TTCAACACAG AATTGTTTTC CACCAGCTTC AATAATTGCG TACATAAATA 1100
ATGTGCCTCC CAAAAAAGAC AAGAAATACT AATTTGATAT TTTCAATATT 1150
GTCAAGTAGG AACTTTATCT TTAGAATGTT AGATGTAACA ATTTTTTTAG 1200
AAAAAAAATA TTTTCAATAC AATAGGAAAA GAGGAAAAAA AAAAAGATTT 1250
TTAGAAAAAA TTTTTATTTC TCCAAAAAAT GCAAAAATAT AAAAAATTCT 1300
AATAGGATAG AAGTTATTAC TGTATTGATT TTCAAGACTT ACTTAAAAAT 1350
TTTTATAAAA AAATTTGCAT TCCCCTCTTC CCAATTCCCA TAGAGAAGAT 1400
TATTTATCCT AACGATTGGT GGACGCTAAG TCCCTGCTGT TTTGATTATA 1450
TATCAAATGT TGAAACAAAT TTTGTTTAGT TTCTTTTTGT ACTCTAAAAA 1500
GAAGACAAAA AATTCTTTAT AAACTGTACA CTCTAAACAA AATAGTTCAC 1550
AATAAACAGC AATACATTAT AATTAATTGG AGGATACTAT TGTCATGAAC 1600
CTGAAACCTT TGAATGACCG TGTTTTAGTA AAACGTCTTG AATCTGAAGA 1650
AAAAACAGCT GGTGGACTCT ATATCCCTGA TACTGCTAAA GAAAAACCAT 1700
CTCGTGGTGA AGTTGTTGCT GTTGGACCTG GTAAACATAC AGATGATGGT 1750
AAATTAATAC CTATGGCTGT AAAAGCAGGA GATACAGTTC TTTTTAATAA 1800
GTATGCAGGA ACAGAAGTAA AGCTTGATGG TGTAGAGCAT CTAGTTATGC 1850
GTGAAGATGA CATCCTAGCT GTTATTACTG GAGAAACTGG CCGCAAGTGA 1900
AAAAGGCGTA AATAAAAAGA TCGGTGATCT TTAATAATTT TATTCAGTTA 1950
TAATGAAAAC ACTAATTACA CGCACTCTCT GAGAATTTTC TCAGAAAACT 2000
ATATTTAACA ATTCTAAAAT CGATATGTTT TTAGGAGGAA AACCCTAATG 2050
GCTTCTAAAG AAATCCTTTT TGATGCTAAA GCCCGTGAAA AACTTTCACG 2100

AGGTGTAGAT AAACTTGCAA ATGCTGTTAA AGTAACACTT GGACCTAAAG 2150
GCCGTAATGT CGTTATTGAA AAGTCTTTTG GTTCCCCAGT TATTACAAAA 2200
GATGGTGTAT CTGTTGCAAA AGAAATTGAA CTTGAAGATA AGTTTGAAAA 2250
TATGGGCGCT CAAATGGTTA AAGAAGTAGC TCCCAAAACT AGCGATATTG 2300
CTGGTGATGG AACTACAACA GCAACAGTCC TTGCACAAGC TATTTATCGT 2350
GAAGGTGTAA AACTTGTAGC AGCTGGTCGT AATCCTATGG CCATTAAACG 2400
TGGCATAGAT AAAGCTGTTG TTGCTGTTAC TAAAGAACTA AGCGACATTA 2450
CAAAGCCTAC TCGTGACCAA AAAGAAATAG CTCAAGTTGG AACCATTTCT 2500
GCAAACTCTG ATACAACAAT AGGTAATATC ATAGCTGAAG CTATGGCTAA 2550
AGTTGGAAAA GGAGGTGTTA TCACAGTTGA GGAAGCTAAA GGTCTTGAAA 2600
CTACATTAGA TGTGGTTGAA GGAATGAAGT TTGACCGTGG CTACCTCTCT 2650
CCATACTTTG TAACTAATCC TGAGAAAATG GTTTGTGAAC TTGATAACCC 2700
TTATATCCTT TGTAATGAGA AAAAGATTAC TAGCATGAAA GACATGCTAC 2750
CAATCTTAGA ACAAGTTGCT AAAGTAAACC GTCCACTCCT TATTATTGCT 2800
GAAGACGTAG AAGGTGAAGC ACTTGCAACA CTTGTAGTCA ATAAGCTCCG 2850
TGGAGCACTC CAAGTTGTAG CCGTAAAAGC TCCTGGTTTT GGTGAACGCC 2900
GTAAAGCTAT GCTTGAAGAT ATTGCTATCC TTACTGGAGG AGAAGCAATA 2950
TTTGAAGATC GTGGTATAAA GCTTGAAAAT GTAAGCTTGT CTTCTTTAGG 3000
AACAGCTAAA CGTGTAGTTA TTGACAAAGA AAATACTACT ATCGTTGATG 3050
GTGCTGGAAA ATCAGAAGAT ATTAAAGCTC GAGTTAAACA AATTCGTGCA 3100
CAAATTGAAG AAACAAGCTC AGATTATGAT CGTGAAAAAC TTCAAGAACG 3150
TCTTGCAAAA CTTGTTGGTG GAGTAGCTGT TATCCATGTT GGAGCTGCTA 3200
CTGAAACTGA AATGAAAGAG AAGAAGGATC GTGTAGAAGA TGCTCTAAAT 3250
GCAACAAGAG CTGCGGTTGA AGAAGGTATT GTCCCTGGTG GTGGTACTGC 3300
TTTTGTCCGC TCCATTAAAG TCCTTGATGA TATTAAACCT GCTGATGATG 3350
ATGAACTTGC TGGACTTAAT ATCATCCGTC GTTCTCTTGA AGAGCCTTTA 3400
CGTCAAATTG CTGCAAATGC TGGCTATGAA GGTTCTATTG TTGTAGAAAA 3450
AGTTCGTGAA CCAAAAGATG GTTTTGGATT TAATGCTGCA TCAGGAGAAT 3500
ATGAAGACCT TATTAAAGCT GGTGTCATTG ATCCTAAAAA AGTTACACGT 3550
ATTGCATTAC AAAATGCAGC ATCAGTAGCC TCCTTACTTC TAACTACAGA 3600
ATGCGCTATT GCTGAAAAAC CAGAACCTAA AAAAGATATG CCTATGCCTG 3650
GCGGTGGTAT GGGTGGTATG GGTGGTATGG ACGGTATGTA CTAGTCCTAT 3700
CTTCAGTACA ACTTAGATGT ATAAAAACCC CAGAAGCAAT GCTTCCGGGG 3750
TTTTATACTT TCAGCATAAA AAATTAATAT TTAATATACA GACACATTAT 3800
TTTGGTATTT ATTATTTATT ATGATCAAAT ATATAGACTG GATACAAAAA 3850
ACAACAATGA TGTTTAAAAA GGCAGGGATA GATTCACCAA AACTCTCTGC 3900
AGAACTTATA TTAAGTCATG TTTTAAATAT TACACGATTA CAAATAATAA 3950

TGACTCCTTT TGAACCTATT CCAACTAATA GCTACTCAAC GCTTAATGAT 4000
ATCATGTTAA GAAGACTCCA TGGAGAACCA ATTGCATATC TCACAGGGAA 4050
AAAAGAATTT TTTTCACGAG AATTTAAAGT CACTCAAGCC ACACTTATCC 4100
CTCGCCCAGA GACAGAGTTA CTTATAGAAT TTGTATTAAA CCATATTAAC 4150
CCAACACAAC AAATATACTT TGCAGACTTA GGTACAGGTA GTGGGTGTAT 4200
TGCAATTACA CTAGCTGCTG AAAGAAAAAA TTGGTTAGGT ATTGCTACTG 4250
ATATCTCTAG TGAAGCATTA AAAATAGCTA AACTTAATAG TTTAAAAAAT 4300
AACACTCATA GTCAACTACA GTTTCTTCAA TCAGATTTTA CACAACCACT 4350
CTGTCTACCC TCTTCATTAG ACTTATATAT CAGTAATCCT CCATATATAA 4400
GTGAAAATGA ACTGACCTCT CTTCCGCATG AAGTAATATC TTTTGAACCT 4450
AAAATAGCTC TTACACCACA TAAATGTATT CATCTTGATG AAATAAATAC 4500
CGTTTTACAC TGCTATAAAA AAATTATTAC CCAAGCAGAG ATATCCCTTA 4550
AGCCTGGAGG AATAATAATT TTAGAACATG GAGCAACACA AGCAGAAGCT 4600
ATCTTATTGT TGTTAAAAAA CAACATATGG ACAAATGTAA TAAGTCATAC 4650
TGATCTTACA AATAAAAATC GTTTTATTAC AGCATATAAG TATAAAATAT 4700
AACTTAATTA TGTTGkagAa AAAACAAAAA ATAAAAATAA GATATtAAaT 4750
ATTTtttttA aTAAAATTAA GCAAtTACTA ATATCTTTTT TTGGrTCGtt 4800
yaTtGsATwA GAAACTTTGG rGGrTrrCTa TGAACAAACA ACCATnCAAC 4850
GGCCAAnTAC ATnnCAGGnT TGGGGTCATA GGGGCCACGC TTTATGTACG 4900
TACAACCCCn ACTGAAATTC TGGnTTGnTT TGGGGGGnAA nTGGGTATCG 4950
CAACnCTnTC CCCCCCCCCT GG 4972

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 569 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 209..569

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
GGTTAAAAAG TAAGGAGAAA AGGTTGGTTA AACCAAGTTT AAAAAATTAA TTTTTTTTTA      60

TTACCCAAAA AAGTTTATTA GATTAAGTAA TATTAATTTG GCCCAAAAAT TTTTTTGGGC     120

ATGGGTTTTT TGCTTTTAAA ATAGAGATGT GTAGGTAACA TTTTTTCCTC CATGAAATTA     180

TTTTTTAGGA GATGTTATCA TGATGGGG AGT TTG TTT ATT GNT GCG AAC AGG         232
                                Ser Leu Phe Ile Xaa Ala Asn Arg
                                  1               5

TAT GAA AAC CCA TAG NAC AGG GNT GGT ACT GTC TCC AAT AAT ATT GCT       280
Tyr Glu Asn Pro  *  Xaa Arg Xaa Gly Thr Val Ser Asn Asn Ile Ala
     10                  15                  20

AAC GCA AAT ACC ATT GGG TAT AAG CAG CAA CAG GTA GTG TTT CAA GAC       328
Asn Ala Asn Thr Ile Gly Tyr Lys Gln Gln Gln Val Val Phe Gln Asp
 25                  30                  35                  40

CTG TTT AGT CAA GAT TTA GCA ATA GGT TTT ACT GGA AGT CAG GGG CCA       376
Leu Phe Ser Gln Asp Leu Ala Ile Gly Phe Thr Gly Ser Gln Gly Pro
                45                  50                  55

AAC CAG GCT GGT ATG GGA GCA CAG GTG GGA AGT GTT CGC ACA ATT TTT       424
Asn Gln Ala Gly Met Gly Ala Gln Val Gly Ser Val Arg Thr Ile Phe
            60                  65                  70

ACA CAG GGT GCT TTT GAA CCT GGC AAT AGT GTA ACA GAT CCT GCT ATT       472
Thr Gln Gly Ala Phe Glu Pro Gly Asn Ser Val Thr Asp Pro Ala Ile
        75                  80                  85

GGT GGA AAA GGT TTT TTT CAG GTT ACA TTA GAG GAT AAA GTA CAC TAT       520
Gly Gly Lys Gly Phe Phe Gln Val Thr Leu Glu Asp Lys Val His Tyr
     90                  95                  100
```

```
ACA CGA GCA GGG AAT TTT CGT TTT ACT CAA GAT GGT TTT TTA AAT GAT C      569
Thr Arg Ala Gly Asn Phe Arg Phe Thr Gln Asp Gly Phe Leu Asn Asp
105                 110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 123 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Ser Leu Phe Ile Xaa Ala Asn Arg Tyr Glu Asn Pro  *  Xaa Arg Xaa
 1               5                  10                  15

Gly Thr Val Ser Asn Asn Ile Ala Asn Ala Asn Thr Ile Gly Tyr Lys
            20                  25                  30

Gln Gln Gln Val Val Phe Gln Asp Leu Phe Ser Gln Asp Leu Ala Ile
        35                  40                  45

Gly Phe Thr Gly Ser Gln Gly Pro Asn Gln Ala Gly Met Gly Ala Gln
    50                  55                  60

Val Gly Ser Val Arg Thr Ile Phe Thr Gln Gly Ala Phe Glu Pro Gly
65                  70                  75                  80

Asn Ser Val Thr Asp Pro Ala Ile Gly Gly Lys Gly Phe Phe Gln Val
                85                  90                  95

Thr Leu Glu Asp Lys Val His Tyr Thr Arg Ala Gly Asn Phe Arg Phe
            100                 105                 110

Thr Gln Asp Gly Phe Leu Asn Asp
```

115 120

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1450 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..414

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1083..1450

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
GA TCT AAA GAG TCT ACA TAT ATT GCC CGA ATT GAA AAT TCT ACA AGT        47
   Ser Lys Glu Ser Thr Tyr Ile Ala Arg Ile Glu Asn Ser Thr Ser
    1               5                  10                  15

GAA AAA ACA CTA AAT GAT CTT GAT ATA CTT TTA AAA GAT GTG ATG TTA        95
Glu Lys Thr Leu Asn Asp Leu Asp Ile Leu Leu Lys Asp Val Met Leu
                20                  25                  30

ACA TCA AAA AAG CAT GAA TCA CGT AGA CTT GCA GAG TCT GTA CAT CAA       143
Thr Ser Lys Lys His Glu Ser Arg Arg Leu Ala Glu Ser Val His Gln
            35                  40                  45

AAT ATT CTT ACC CAC CTT ATA CAA AAA AAT TAT AAT ACT CAC AAT GGT       191
```

```
Asn Ile Leu Thr His Leu Ile Gln Lys Asn Tyr Asn Thr His Asn Gly
          50                  55                  60

GGG ATA AAA TCT GCA CCT TTT CAT GTT CTT ATA GGA CCC AAA ATA CCA      239
Gly Ile Lys Ser Ala Pro Phe His Val Leu Ile Gly Pro Lys Ile Pro
     65                  70                  75

AGT ATT CTT GTT GAA GTA GGT TAC TGT AGT AAT AAA GCT GAA GCA CAG      287
Ser Ile Leu Val Glu Val Gly Tyr Cys Ser Asn Lys Ala Glu Ala Gln
 80                  85                  90                  95

CGT CTG GCA TCT AGT AAT TAC CAA AAA GCA TTA ATA GAA GGA TTA GCT      335
Arg Leu Ala Ser Ser Asn Tyr Gln Lys Ala Leu Ile Glu Gly Leu Ala
                100                 105                 110

AAA GGT ATT TTC TGT TAC CTA AAA AAA CTA CAT CAC CTT GAT ATT TAC      383
Lys Gly Ile Phe Cys Tyr Leu Lys Lys Leu His His Leu Asp Ile Tyr
            115                 120                 125

TCT AGT TTT ATY CTA TCT AAT TGC ACT TAA T AGCTTGGACA ATTATTATAT      434
Ser Ser Phe Ile Leu Ser Asn Cys Thr  *
        130                 135

GAAGGGTATC CATGTGAAGG TACCTGGTTA AGCTTTTAAA TGTAAAAATT ATGCAACCAT    494

ACYTTATTCC TTCAGAGGAG CTTCATTATG AAAGTAAAAA CTCTTTCCAT GGCTATTTTA    554

GCTTGTTTAT TAGTAGCTAA CAGTGCATTT TCGGCTGACT TCCCTATTGG TGTCTTTAAT    614

TCTCAATCCA TTGCCATGGA GAGTGAAGCA GCTAAGGCCG CTCAAAAAAA ATTACAATCA    674

GAATTTGGTA ATGAAAAAAC ACAACTTGAA AACAAGCAAA AGWTTGCMAA CAAAAGCTGA    734

TGATTTACAA GCTWAGTCAG CAGCTATGTY TAACCAAGCA CGTGAAGATA AACAAAGAGA    794

ATTTCTTGAA CTTCGTCGTA ATTTCGAAGA AAAATYTCGT GACTTTGCAA TACGTGTCGA    854
```

```
ACAAGCTGAA AACACATTAC GTCAATATNT AGCTGAACAA ATNTATNTTG CTGCTGAAAC      914

TATAGCAAAA AAGAAAGGGT TAAACTTGTT TTGATAGTGT TAGGGAAGTG TAATGTACCT      974

TGAAAAAAAT TTAGATATTA CAAAGAAATT YTTGAAGCCA TAAATGCTGC ATGGAAAAAA     1034
GGTGGAAGTA AACTTCCAGA GATGGCAAAC CGGAAAAAAT AACAG ATG CCC CAG TAT      1091
                                                 Met Pro Gln Tyr
                                                  1

AAA CTT TCA GAA ATT GCT AAA CTT TTA AAC TTA ACA TTA CAA GGT GAT        1139
Lys Leu Ser Glu Ile Ala Lys Leu Leu Asn Leu Thr Leu Gln Gly Asp
 5                  10                  15                  20

GAT ATT GAA GTT GTA GGC GTA AAT ACA CTT CAA GAT GCA TCA CCA AAT        1187
Asp Ile Glu Val Val Gly Val Asn Thr Leu Gln Asp Ala Ser Pro Asn
                25                  30                  35

GAG ATA AGT TTT CTA GCA AAT GCT AAA TAT ATT CAC CAG CTT GTT TTG        1235
Glu Ile Ser Phe Leu Ala Asn Ala Lys Tyr Ile His Gln Leu Val Leu
            40                  45                  50

TCA CAG GCT GGT GCT ATT ATT CTT TCA AAA GAA TAT GCT AGT CGT GTT        1283
Ser Gln Ala Gly Ala Ile Ile Leu Ser Lys Glu Tyr Ala Ser Arg Val
        55                  60                  65

CCA CGA GCA CTA ATC AGT ACT GAA CCA TAT AGA GAT TTT GGT AGA GTT        1331
Pro Arg Ala Leu Ile Ser Thr Glu Pro Tyr Arg Asp Phe Gly Arg Val
    70                  75                  80

CTT TCT TTA TTC TCT ATA CCT CAA GGA TGT TTT GAT GGT ATA AGT CAT        1379
Leu Ser Leu Phe Ser Ile Pro Gln Gly Cys Phe Asp Gly Ile Ser His
 85                  90                  95                  100

CAA GCT TAT ATA CAC CCT ACA GCA CAA GTC TCT AAA ACA GCT ACT ATC        1427
Gln Ala Tyr Ile His Pro Thr Ala Gln Val S r Lys Thr Ala Thr Ile
                105                 110                 115
```

TAT CCT TTn GTT TTT ATA GGA TC 1450
Tyr Pro Xaa Val Phe Ile Gly
120

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 137 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Ser Lys Glu Ser Thr Tyr Ile Ala Arg Ile Glu Asn Ser Thr Ser Glu
1 5 10 15

Lys Thr Leu Asn Asp Leu Asp Ile Leu Leu Lys Asp Val Met Leu Thr
20 25 30

Ser Lys Lys His Glu Ser Arg Arg Leu Ala Glu Ser Val His Gln Asn
35 40 45

Ile Leu Thr His Leu Ile Gln Lys Asn Tyr Asn Thr His Asn Gly Gly
50 55 60

Ile Lys Ser Ala Pro Phe His Val Leu Ile Gly Pro Lys Ile Pro Ser
65 70 75 80

Ile Leu Val Glu Val Gly Tyr Cys Ser Asn Lys Ala Glu Ala Gln Arg
85 90 95

Leu Ala Ser Ser Asn Tyr Gln Lys Ala Leu Ile Glu Gly Leu Ala Lys
100 105 110

Gly Ile Phe Cys Tyr Leu Lys Lys Leu His His Leu Asp Ile Tyr Ser

115 120 125

Ser Phe Ile Leu Ser Asn Cys Thr *
130 135

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 123 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Pro Gln Tyr Lys Leu Ser Glu Ile Ala Lys Leu Leu Asn Leu Thr Leu
1 5 10 15

Gln Gly Asp Asp Ile Glu Val Val Gly Val Asn Thr Leu Gln Asp Ala
20 25 30

Ser Pro Asn Glu Ile Ser Phe Leu Ala Asn Ala Lys Tyr Ile His Gln
35 40 45

Leu Val Leu Ser Gln Ala Gly Ala Ile Ile Leu Ser Lys Glu Tyr Ala
50 55 60

Ser Arg Val Pro Arg Ala Leu Ile Ser Thr Glu Pro Tyr Arg Asp Phe
65 70 75 80

Gly Arg Val Leu Ser Leu Phe Ser Ile Pro Gln Gly Cys Phe Asp Gly
85 90 95

Ile Ser His Gln Ala Tyr Ile His Pro Thr Ala Gln Val Ser Lys Thr

```
            100                 105                 110

Ala Thr Ile Tyr Pro  *  Val Phe Ile Gly
        115                 120
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 559 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..557

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
GA TCA AAG CCG CAT TTA CNG CAA GAG TTA GAA ATT GAA GTT TTG AAA          47
   Ser Lys Pro His Leu Xaa Gln Glu Leu Glu Ile Glu Val Leu Lys
    1               5                  10                  15

AAA GAA GAC TTT GGG CGT CAT ATT GTT AAA TTA TGC TGG AAA GGT TCT         95
Lys Glu Asp Phe Gly Arg His Ile Val Lys Leu Cys Trp Lys Gly Ser
                20                  25                  30

TTA TCA AAT ATC TTT TTT TCC TAT GGG GAT ATC CCG CAC CCA CCT TAT        143
Leu Ser Asn Ile Phe Phe Ser Tyr Gly Asp Ile Pro His Pro Pro Tyr
            35                  40                  45

ATA CAT CAA AGT AAT AAG GTT CAG GAT AAG GAA AGA TAT CNT ACN GTA        191
```

```
Ile His Gln Ser Asn Lys Val Gln Asp Lys Glu Arg Tyr Xaa Xaa Val
          50                  55                  60

TAC TCT ATA TTA CAT AAN CTG GGT TCT GTA GCA GCT CCT ACA GCT GGA      239
Tyr Ser Ile Leu His Xaa Leu Gly Ser Val Ala Ala Pro Thr Ala Gly
      65                  70                  75


TTA CNC TTT TCT GAA ACT AGC CGT NAT AAA TTA CAC AAA NAT GGT ATT      287
Leu Xaa Phe Ser Glu Thr Ser Arg Xaa Lys Leu His Lys Xaa Gly Ile
 80                  85                  90                  95

AGT TGG GCA TAA ATC CCT CTT CAC GTG GGA TAT GGA ACA TTC AGT CCC      335
Ser Trp Ala  *  Ile Pro Leu His Val Gly Tyr Gly Thr Phe Ser Pro
                100                 105                 110

GTC CTC TGC AAT GAC ATC CCA AAA CAT CTT ATC CNT TCT GAG TTT GTT      383
Val Leu Cys Asn Asp Ile Pro Lys His Leu Ile Xaa Ser Glu Phe Val
            115                 120                 125

CAC TTT CCT GAA ACT ACN TTT TCC ACT ATA TTA AAT GCA CGG TTT GCA      431
His Phe Pro Glu Thr Xaa Phe Ser Thr Ile Leu Asn Ala Arg Phe Ala
        130                 135                 140

NGG GAA TAC CTA TGT TCT GCC ATA GGG GAC CCA CTG TTG TCC CCA CCA      479
Xaa Glu Tyr Leu Cys Ser Ala Ile Gly Asp Pro Leu Leu Ser Pro Pro
    145                 150                 155

TTG GAN GGG TGT TAT CTT ACC CCT TTC GCC CGG GGT TCC CCT CCC CAA      527
Leu Xaa Gly Cys Tyr Leu Thr Pro Phe Ala Arg Gly Ser Pro Pro Gln
160                 165                 170                 175

CCC TAT TCC ATT GNG TTT TCC TCT CAA ATT AT                           559
Pro Tyr Ser Ile Xaa Phe Ser Ser Gln Ile
                180                 185
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 185 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Ser Lys Pro His Leu Xaa Gln Glu Leu Glu Ile Glu Val Leu Lys Lys
1 5 10 15

Glu Asp Phe Gly Arg His Ile Val Lys Leu Cys Trp Lys Gly Ser Leu
20 25 30

Ser Asn Ile Phe Phe Ser Tyr Gly Asp Ile Pro His Pro Pro Tyr Ile
35 40 45

His Gln Ser Asn Lys Val Gln Asp Lys Glu Arg Tyr Xaa Xaa Val Tyr
50 55 60

Ser Ile Leu His Xaa Leu Gly Ser Val Ala Ala Pro Thr Ala Gly Leu
65 70 75 80

Xaa Phe Ser Glu Thr Ser Arg Xaa Lys Leu His Lys Xaa Gly Ile Ser
85 90 95

Trp Ala * Ile Pro Leu His Val Gly Tyr Gly Thr Phe Ser Pro Val
100 105 110

Leu Cys Asn Asp Ile Pro Lys His Leu Ile Xaa Ser Glu Phe Val His
115 120 125

Phe Pro Glu Thr Xaa Phe Ser Thr Ile Leu Asn Ala Arg Phe Ala Xaa
130 135 140

Glu Tyr Leu Cys Ser Ala Ile Gly Asp Pro Leu Leu Ser Pro Pro Leu
145 150 155 160

Xaa Gly Cys Tyr Leu Thr Pro Phe Ala Arg Gly Ser Pro Pro Gln Pro
165 170 175

Tyr Ser Ile Xaa Phe Ser Ser Gln Ile
180 185

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 477 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..294

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

T ATA AAA CAT TAG CGN CTT TNG TAT TTG GAC TTC AAA AAA ATT TTT 46
Ile Lys His * * Leu * Tyr Leu Asp Phe Lys Lys Ile Phe
1 5 10 15

AAT TAT ATA GGA GAA CAT TCA CCA TTA AAA CGT AAT GTA ANT ATG GAA 94
Asn Tyr Ile Gly Glu His Ser Pro Leu Lys Arg Asn Val * Met Glu
20 25 30

GAT GTA GGT AAA TCT GCT GTT TTT TTA GCT TCA GAC CTN TCA TCA GGA 142
Asp Val Gly Lys Ser Ala Val Phe Leu Ala Ser Asp * Ser Ser Gly

```
                35                  40                  45

GTA ACC GGT GAA TTN TTT TTG TTG ATG CTG GNA CAA TAA TTT AGG TAT      190
Val Thr Gly Glu  *  Phe Leu Leu Met Leu  *  Gln  *  Phe Arg Tyr
         50                  55                  60

TTA ACC ATA CAT GCT TTA TAC AAC ATA TTG TGA GTT ACA ATA GCC ATA      238
Leu Thr Ile His Ala Leu Tyr Asn Ile Leu  *  Val Thr Ile Ala Ile
     65                  70                  75

ACA CAT TTA TAT TCT ATA TAA TAA CAG TAG AAT AAT AAT AGA ATA TTT      286
Thr His Leu Tyr Ser Ile  *   *  Gln  *  Asn Asn Asn Arg Ile Phe
 80                  85                  90                  95

TTT ATG ACC ATTTGTATCT ATACAATAGT AAATAGATTA ATACATATAA GACTATATTC   344
Phe Met Thr

TTTTTGAGAG CAACTTAAAG GAGCGGTTAT GGCTTTAGTT ACAAAAGAAG AAGTACTTCA   404

ATACCATAGT GAACCCCGAC CAGGTAAACT TGAAGTATTT TCTATAAAAC CATGTAAAAC   464

ACAAAAAGAT CC                                                       477
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Ile Lys His  *  Xaa Leu Xaa Tyr Leu Asp Phe Lys Lys Ile Phe Asn
```

1 5 10 15

Tyr Ile Gly Glu His Ser Pro Leu Lys Arg Asn Val Xaa Met Glu Asp
20 25 30

Val Gly Lys Ser Ala Val Phe Leu Ala Ser Asp Xaa Ser Ser Gly Val
35 40 45

Thr Gly Glu Xaa Phe Leu Leu Met Leu Xaa Gln * Phe Arg Tyr Leu
50 55 60

Thr Ile His Ala Leu Tyr Asn Ile Leu * Val Thr Ile Ala Ile Thr
65 70 75 80

His Leu Tyr Ser Ile * * Gln * Asn Asn Asn Arg Ile Phe Phe
85 90 95

Met

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..525

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
G GAA TTG TTA GTA TTC TCC CAG AAC AGA AGC CAA AAT ATT TGG CTA          46
  Glu Leu Leu Val Phe Ser Gln Asn Arg Ser Gln Asn Ile Trp Leu
    1               5                  10                  15

CTT ACA TTA CCT ATT TTT GTG TTA GGT ATA GCA CAA GGT ATA TCA TTT        94
Leu Thr Leu Pro Ile Phe Val Leu Gly Ile Ala Gln Gly Ile Ser Phe
                20                  25                  30

CCT TTA GTA AAC AGC CAC ATT ACA TCA CTT GCA CCA ACA TCC AAC AGA       142
Pro Leu Val Asn Ser His Ile Thr Ser Leu Ala Pro Thr Ser Asn Arg
            35                  40                  45

GCT ATT GTT ATG GCT ATA AAC AGT ACA TTT ATG AGG TTA AGT CAG AGT       190
Ala Ile Val Met Ala Ile Asn Ser Thr Phe Met Arg Leu Ser Gln Ser
        50                  55                  60

ATT TCG CAA ATG GTT TTT GGT ATT GGA TGG TCA TTT TTT GGT TGG CCT       238
Ile Ser Gln Met Val Phe Gly Ile Gly Trp Ser Phe Phe Gly Trp Pro
    65                  70                  75

GGT CCT TTT ATA TTT GGT CTT TTT ACT TCT ATT ATA TTA GCC CTC TTA       286
Gly Pro Phe Ile Phe Gly Leu Phe Thr Ser Ile Ile Leu Ala Leu Leu
80                  85                  90                  95

ATT ATG AAG TAT TTT CAA GAT GTA ACC CAA TAT CAC CTA TTT TTG ATA       334
Ile Met Lys Tyr Phe Gln Asp Val Thr Gln Tyr His Leu Phe Leu Ile
                100                 105                 110

AGT AGT AAA TTT TAT TAT TAA AAA GCT TAG TTA GTT AAG ATT ACA TAT       382
Ser Ser Lys Phe Tyr Tyr  *  Lys Ala  *  Leu Val Lys Ile Thr Tyr
            115                 120                 125

ATT ATA TAC AAT TAC TAT AAC ATT AAC TAA TTA CTA ACT ATT ACT TCC       430
Ile Ile Tyr Asn Tyr Tyr Asn Ile Asn  *  Leu Leu Thr Ile Thr Ser
        130                 135                 140

AAT TGA TTA ATT GAT GCT ATT TAA AGA GGA TAT ATT AAT GAT GTC ATG       478
```

```
Asn  *  Leu Ile Asp Ala Ile  *  Arg Gly Tyr Ile Asn Asp Val Met
    145                 150                 155

GCT CAC AAT AGG TGT TAT CCT TGG ATT AGT GCA TGG GAT CCA GGT CC      525
Ala His Asn Arg Cys Tyr Pro Trp Ile Ser Ala Trp Asp Pro Gly
160                 165                 170
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 174 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Glu Leu Leu Val Phe Ser Gln Asn Arg Ser Gln Asn Ile Trp Leu Leu
  1               5                  10                  15

Thr Leu Pro Ile Phe Val Leu Gly Ile Ala Gln Gly Ile Ser Phe Pro
             20                  25                  30

Leu Val Asn Ser His Ile Thr Ser Leu Ala Pro Thr Ser Asn Arg Ala
         35                  40                  45

Ile Val Met Ala Ile Asn Ser Thr Phe Met Arg Leu Ser Gln Ser Ile
     50                  55                  60

Ser Gln Met Val Phe Gly Ile Gly Trp Ser Phe Phe Gly Trp Pro Gly
 65                  70                  75                  80

Pro Phe Ile Phe Gly Leu Phe Thr Ser Ile Ile Leu Ala Leu Leu Ile
                 85                  90                  95
```

Met Lys Tyr Phe Gln Asp Val Thr Gln Tyr His Leu Phe Leu Ile Ser
100 105 110

Ser Lys Phe Tyr Tyr * Lys Ala * Leu Val Lys Ile Thr Tyr Ile
115 120 125

Ile Tyr Asn Tyr Tyr Asn Ile Asn * Leu Leu Thr Ile Thr Ser Asn
130 135 140

* Leu Ile Asp Ala Ile * Arg Gly Tyr Ile Asn Asp Val Met Ala
145 150 155 160

His Asn Arg Cys Tyr Pro Trp Ile Ser Ala Trp Asp Pro Gly
165 170

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 846 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TATTTACTCG CGCGGCCGGG CGTCTTACAC AAATGGATCC CTTGCANTAA TCCAAGGATA 60

ACNCCTATTG TGANCCATGA ACATCATCAN NATATCCTCT TTANATAGCA TCNANNNNTC 120

AANNGGAATT AACAGTTACT ANNTAGTTAA TGTCATAGTA ATTGTCNATA ATATATGTAA 180

TCTTAACTAA CTAAGCTNNT TAATAATAAA ATTNACTACT TATCAANAAT AGGTGATATN 240

GGGTTACATC TTGAAAATAC TTNCCATAAT TANGAGGGCT AATATAATNG AANTAAAAAG 300

ACCANATATA AAAGGACCAG GCCAACCAAA AAATGACCAT CCAATACCNA AAACAATTGG 360

CGAAAATACT CTGACTTAAC CTCANAAATG TACTGTTTAT AGCCATATCA ATAGCTCTGT 420

TGGATGTNGG NGCAATTGAT GTAATGTGGC TGTNTACTAN ANGAAATGAT NTACCTCGTG 480

CTATNCCTAN NACAANAATA NGTAATGTAA GTANCCNAAT ATCTTGGCTT TGTAATGGGA 540

GAATAATNNC AAGTCCTTGG GAAATNAANT TACNNCCAGC CAGCTATNNT AAGCAGTTCT 600

NTGGTGACTA TACGTCCTAC TNAANTCGTG CCAAAGATTA AATANNCGAT AATCGCNCTN 660

CCTAAANCAN GCAATACTAA AATGGTTTCT NCCTANCTTG GNATANGGTG GAAGCNCGGA 720

CAGAATTNAN TTCGCNANTT TANANNGGAA NATNCGTNAA NTTANTCGGG GCCCANNCCN 780

AAATTCCTNA NTCNATANAN NAACTNNCTN CTNTAAAANG GCCNACTGGA NTNGTTAAAT 840

GAAATA 846

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 855 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GATTNTTTAT CGATCACTNT AGACGCGATT TGGGNAACAC TTACCTGGTA NCCACCCGGG 60

TGGAAAAATC GATGGGCCCG CGGCCGCTCT AGAAGTACTC TCGAGAAGCT TTTTGAATTC 120

TTTGGATCCT CAACACAGGG TATGGATTAA AACAACTTTA GCTCTAACAG GAGCATTTTA 180

TAATATATTC CCTGGTAGAA CAATATCTAC TCAAGAAAAT CTGTCTATTG GTTTTCAACT 240

AAAAAAAACT TTTAAACCTT TTCATTGGAC CATCTTACTC TTAGATGAAC ATTATATGTC 300

TTCGCCAAGA ATTGCAGCAG CAATTATGCC TGCACAGCTT GCTGGAGTTA AAAACATTAT 360

AGCTGTTTGG ACCAGTAAAA ATAACCGACT GACCGCTGAA AAAATCTCAC CTGCTTTACT 420

AACAACATTA GAACTTTCAG GAGTTAACAT AGCCCTAACA CTTACCCACA CTGAAACTGA 480

ACTTCTTATT CATCAATTAA TGAAAATAGG TATTGGAAAC CTGTTATATT TTTTAAAAGA 540

AGAAGACATA CTACATATAT CTACTATACC TGTACTACCT TTCTGGAAAG AATATACTTC 600

TCATCGACTT GTTATAGAAA AAGATGCTGG CNTTAATACA GAAATCCTCC AATGGGCNCA 660

TCCTCATTCA ATTATTGAAC AAATAGCAAC AGAACCATAC TCTGAAANAT ATCCCAGATG 720

CACTTTACTG TGCTAGCTCA TCCANTAAAA ACTATNCTCA TANAGNATCC CCAGAATTTT 780

TCATNATGGA CTTGAACCTA TTTGGATTCA NCCCAACNCT TCCTCCAANC CTCCTTTCTC 840

CATACACCAT GGGGA 855

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1082 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TATCTNGTTG ANTCAATAAA ACTTTTGGGG CCCNTNAAAN TTTCATNANN AAAAAAACAA 60

NATTNCTGGG GGNCCCNTCC CAAAAAANNC AATCANTNNG AANCTTGNCT TCTTATTNNG 120

NTTTTNANAC TATAATATNT NTTATCNATA ATNNATCNNT ATACTNATTT CTNATTCANT 180

NACANNGGNN AGNAANNTTA ATCTNAAANA CTNCNAAGGG GGNNNTNATA NTNTTTNTTT 240

NTTTNTCCCN TNNAATNNAT AACCNNNCAC CCNNATTANT TNNAATNNAT ACCATANCNN 300

CCTTTCAAAC TGTACACATA NTANNNAANN ACACTCNANC NTTTTNCATC CTCTCTANTN 360

CCNACTCCNA TNNANCTNTT CCCCCATNCC TATNTNTCNC TGCTTCCCAG NTTNNACNTN 420

NCTTNNTTTC ACANTATTCC TATCCAANCT AACATNTNTN NTNTCNTNCT CCTTNTNTNT 480

TATNTNTTTC TNNTACCTNN CACTGACANT CTATNANTNA NNTCNNATAC TNNTATANCT 540

NTANGCNANT NTATCTANAA NTNTANCNNN NNATCNTNAC NGCCGTNNAT NTNNNNNCAN 600

TTANNTANNN CTANCNTNNC CAANNNCNTA TNTATNAATA ACNACTATCC NATATTNNAT 660

TNNNTNNTNT CNTANNCAAA TNATTTANGC NCACNNCACT ANGTNATATN ANNATTNTAT 720

ATTNTGAANC TTCTNGGCTT CNCNAATANT ACCANTNNNC ANCNTCNNNT NCATCTNNNT 780

NTACTTCNTA CCATANCGCT CTCNAGNNTC ACTACTTCTA NTAGTNATCN TCTACTGCCN 840

ATGGCNNNNN GCNNNNCGAN AGNTATNCAC NTACANTNNC NTCTACTATN TANATCTANN 900

NCNTCCGNNG CCTNCNGTAC GNNTNGGCNA ANTCGNNTAC TTTNCNTNTA TCTAGTCNCA 960

TCAGNNNTNG ANTCCTCAAN CNNGCTCTAN TTACATGTNN NNTNATGCNC TANANCGNNA 1020

CNTCTATCCT TCNANTCTGC NCTNANTNTA TANACTCTNN NNNATCNNCN AANCTATNTC 1080

CC 1082

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 354 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) SEQUENCE DESCRIPTION: SEQ ID NO:20

CTCCCNTNNC NCTAAGTGGA NTCGCGCGCT GCAGGTCGAC ACTAGTGGAT CTTGATATAC 60

TTTTAAAAGA TGTGATGTTA ACATCAAAAA AGCATGAATC ACGTTAGACT TGCAGAGTCT 120

GTACATCAAA ATATTCTTTA CCCACCTTAA TACGAAAANA AATNNTTATN CNCCNCNATG 180

GGTGGGGNTN AAATCCTNGC CCCNTTNCCC TGTTCNTTTA GGGAACCCCC NAATTCCCCN 240

NGTTATTCCT CTGTTTGAAA NTTCTGGTTN CCCGGCCCTN TNACCAANAG CTTGANNNCC 300

NCCCCGTCCT GGGGCATCCT CNTGTTTATT TTCCCTCNAN CNCCCCCTTN ACTN 354

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 477 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) SEQUENCE DESCRIPTION: SEQ ID NO:21

GGATCTTTTT GTGTTTTACA TGGTTTTATA GGAAATACTT CAAGTTTACC TGGTCGGGGT 60
TCACTATGGT ATTGAAGTAC TTCTTCTTTT GTNACTAAAG CCATAACCGC TCCTTTAAGT 120
TGTTCTCAAA AAGAATATAG TCTTATATGT ATTAATCTAT TTACTATTGT ATAGATACAA 180
TAGGTCATAA AAAATATTCT ATTATTATTC TACTGTTATT ATATAGAATA TAAATGTGTT 240
ATGGCTATTG TAACTCACAA TATGTTGTAT AAAGCATGTA TGGTTAAATA CCTAAATTAT 300
TGTNCCAGCA TCAACAAAAA NAATTCACCG GTTACTCCTG ATGANAGGTC TGAAGCTAAA 360
AAAACAGCAG ATTTACCTAC ATCTTCCATA NTTACATTAC GTTTTAATGG TGAATGTTCT 420
CCTATATAAT TAAAAATTTT TTTGAAGTCC AAATACNAAA GNCGCTAATG TTTTATA 477

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 568 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) SEQUENCE DESCRIPTION: SEQ ID NO:22

GATCATTTAA AAAACCATCT TGAGTAAAAC GAAAATTCCC TGCTCGTGTA TAGTGTACTT 60

TATCCTCTAA TGTAACCTGA AAAAAACCTT TTCCACCAAT AGCAAGATCT GTTACACTAT 120

TGCCAGGTTC AAAAGCACCC TGTGTAAAAA TTGTGCGAAC ACTTCCAACC TGTGCTCCCA 180

TACCAGCCTG GTTTGGCCCC TGACTTCCAG TAAAACCTAT TGCTAAATCT TGACTAAACA 240

GGTCTTGAAA CACTACCTGT TGCTGCTTAT ACCCAATGGT ATTTGCGTTA GCAATATTAT 300

TGGAGACAGT ACCANCCCTG TNCTATGGGT TTTCATACCT GTTGGCANCA ATAAACAAAC 360

TCCCCATCAT GATAACATCT CCTAAAAAAT AATTTCATGG NGGNAAAAAT GTTACCTACA 420

CATCTCTATT TTNAAAGCAA AAAACCCATG CCCAANAAAA TTTTTGGGCC NAATTAATAT 480

ACTTAATCTA ATAAACTTTT TTGGGTAATN AAAAAAAATT AATTTTTTAA ACTTGGTTTN 540

ACCAACCTTT TCTCCTTACT TTTTAACC

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 477 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(iii) SEQUENCE DESCRIPTION: SEQ ID NO:23

GGTACCCCAC CCGGGTGGAA AATCGATGGG CCCGCGGCCG CTCTAAAANT 50

ACTCTCGAGA AGCTTTTTGA ATTCTTTGGA TCCCCAGGAA TAACTTGTTG 100

ACGGAATTTT ACATTTTCTA TCCCTGCAAA TANAAAAACT TTACCTTGTA 150

GTTCATTAAT AGGAAAAGAT TGGAGTACTG TGATTCCACC TGATTGCGCC 200

ATAGCTTCTA AAATTAGAAC TCCAGGCATG ACAGGAAATC CAGGGGAAAT 250

GACCCNGAAA AAATGGTTCA TTAATACTAA CATTTTTATA AGCTTTAATA 300

TATTTGCCAG CATTAAATTC AATAACTCTA TCTACAATTA AAAAGGGATA 350

ACGGTGGGGA ATTTACTGTA AAATTTCTTG GATATTTTGG AGGTATGGAT 400

GGGGACATTA ATTTTCCTAT ATATATGCTC TTTTTCTTTT CNAAAATTTT 450

TCAGCTTTTT TATCCCNTAA AAACCTC 467

CLAIMS:

1. A vaccine composition for the prophylaxis or treatment of infection in an animal or bird by *Lawsonia intracellularis* or related microorganism, said vaccine composition comprising an immunogenic, non-pathogenic form of *L. intracellularis* or related microorganism or an immunogenic component thereof and one or more carriers, diluents and/or adjuvants suitable for veterinary or pharmaceutical use.

2. A vaccine composition according to claim 1 wherein the composition is for the prophylaxis or treatment of infection in pigs by *L. intracellularis* or related microorganism.

3. A vaccine composition according to claim 2 wherein the non-pathogenic form of *L. intracellularis* or related microorganism is an attenuated strain of the microorganism.

4. A vaccine composition according to claim 2 wherein the non-pathogenic form of *L. intracellularis* or related microorganism is a killed preparation of the microorganism.

5. A vaccine composition according to claim 4 wherein the non-pathogenic form of *L. intracellularis* is a formalin-killed preparation of the microorganism.

6. A vaccine composition according to claim 1 or 2 wherein said composition comprises a peptide, polypeptide, protein, carbohydrate, lipid or nucleic acid molecule or a combination thereof from *L. intracellularis* or related microorganism in an amount effective to induce a protective immune response agent *L. intracellularis* or related microorganism.

7. A vaccine composition according to claim 6 wherein the composition comprises a peptide, polypeptide, protein or a derivative thereof from *L. intracellularis* or related microorganism.

8. A vaccine composition according to claim 7 wherein the peptide, polypeptide or protein is in recombinant form.

9. A vaccine composition according to claim 7 or 8 wherein the composition comprises a refolding/heatshock protein, a flagellar basal body rod protein, S-adenosylmethionine: tRNA ribosyltransferase-isomerase, autolysin, enoyl-(acyl-carrier-protein) reductase or a glucarate transporter or derivative thereof.

10. A vaccine composition according to claim 9 wherein the protein is GroEL having an amino acid sequence set forth in SEQ ID NO:2 or is a protein having at least about 40% similarity thereto.

11. A vaccine composition according to claim 9 wherein the protein is GroES having an amino acid sequence set forth in SEQ ID NO:4 or is a protein having at least about 40% similarity thereto.

12. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:1 or a sequence having at least about 40% similarity thereto.

13. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:3 or a sequence having at least about 40% similarity thereto.

14. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:5 or a sequence having at least about 40% similarity thereto.

15. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:6

or a sequence having at least about 40% similarity thereto.

16. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:8 or a sequence having at least about 40% similarity thereto.

17. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:11 or a sequence having at least about 40% similarity thereto.

18. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:13 or a sequence having at least about 40% similarity thereto.

19. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:15 or a sequence having at least about 40% similarity thereto.

20. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:17 or a sequence having at least about 40% similarity thereto.

21. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:18 or a sequence having at least about 40% similarity thereto.

22. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:19 or a sequence having at least about 40% similarity thereto.

23. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:20 or a sequence having at least about 40% similarity thereto.

24. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:21 or a sequence having at least about 40% similarity thereto.

25. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:22 or a sequence having at least about 40% similarity thereto.

26. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein having an amino acid sequence of SEQ ID NO:7 or a sequence having at least 40% similarity.

27. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein having an amino acid sequence of SEQ ID NO:9 or a sequence having at least 40% similarity.

28. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein having an amino acid sequence of SEQ ID NO:10 or a sequence having at least 40% similarity.

29. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein having an amino acid sequence of SEQ ID NO:12 or a sequence having at least 40% similarity.

30. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein having an amino acid sequence of SEQ ID NO:14 or a

sequence having at least 40% similarity.

31. A vaccine composition according to claim 8 wherein the composition comprises a peptide, polypeptide or protein having an amino acid sequence of SEQ ID NO:16 or a sequence having at least 40% similarity.

32. A method for vaccinating an animal or bird against infection by *L. intracellularis* or related microorganism or treating an animal or bird infected by *L. intracellularis,* said method comprising administering to said animal or bird an effective amount of a non-pathogenic form of *L. intracellularis* or related microorganism or an immunogenic component thereof for a time and under conditions sufficient to induce a protective immune response against *L. intracellularis* or related microorganism.

33. A method according to claim 32 wherein the animal is a pig.

34. A method according to claim 33 wherein the non-pathogenic form of *L. intracellularis* or related microorganism is an attenuated strain of the microorganism.

35. A method according to claim 33 wherein the non-pathogenic form of *L. intracellularis* or related microorganism is a killed preparation of the microorganism.

36. A method according to claim 35 wherein the non-pathogenic form of *L. intracellularis* is a formalin-killed preparation of the microorganism.

37. A method according to claim 32 and 33 wherein said immunogenic component comprises a peptide, polypeptide, protein, carbohydrate, lipid or nucleic acid molecule or a combination thereof from *L. intracellularis* or related microorganism in an amount effective to induce a protective immune response against *L. intracellularis* or related microorganism.

38. A method according to claim 37 wherein said immunogenic component comprises a

peptide, polypeptide, protein or a derivative thereof from *L. intracellularis* or related microorganism.

39. A method according to claim 38 wherein the peptide, polypeptide or protein is in recombinant form.

40. A method according to claim 29 or 30 wherein the immunogenic component is a refolding/heatshock protein, a flagellar basal body rod protein, S-adenosylmethionine: tRNA ribosyltransferase-isomerase, autolysin, enoyl-(acyl-carrier-protein) reductase or a glucarate transporter or derivative thereof.

41. A method according to claim 40 wherein the protein is GroEL having an amino acid sequence set forth in SEQ ID NO:2 or is a protein having at least about 40% similarity thereto.

42. A method according to claim 40 wherein the protein is GroES having an amino acid sequence set forth in SEQ ID NO:4 or is a protein having at least about 40% similarity thereto.

43. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:1 or a sequence having at least about 40% similarity thereto.

44. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:3 or a sequence having at least about 40% similarity thereto.

45. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:5 or a sequence having at least about 40% similarity thereto.

46. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:6 or a sequence having at least about 40% similarity thereto.

47. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:8 or a sequence having at least about 40% similarity thereto.

48. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:11 or a sequence having at least about 40% similarity thereto.

49. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:13 or a sequence having at least about 40% similarity thereto.

50. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:15 or a sequence having at least about 40% similarity thereto.

51. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:17 or a sequence having at least about 40% similarity thereto.

52. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:18 or a sequence having at least about 40% similarity thereto.

53. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:19

or a sequence having at least about 40% similarity thereto.

54. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:20 or a sequence having at least about 40% similarity thereto.

55. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:21 or a sequence having at least about 40% similarity thereto.

56. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein encoded by a nucleotide sequence comprising SEQ ID NO:22 or a sequence having at least about 40% similarity thereto.

57. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein comprising an amino acid sequence set forth in SEQ ID NO:7 or having at least 40% similarity thereto.

58. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein comprising an amino acid sequence set forth in SEQ ID NO:9 or having at least 40% similarity thereto.

59. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein comprising an amino acid sequence set forth in SEQ ID NO:10 or having at least 40% similarity thereto.

60. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein comprising an amino acid sequence set forth in SEQ ID NO:12 or having at least 40% similarity thereto.

61. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein comprising an amino acid sequence set forth in SEQ ID NO:14 or having at least 40% similarity thereto.

62. A method according to claim 38 wherein the immunogenic component comprises a peptide, polypeptide or protein comprising an amino acid sequence set forth in SEQ ID NO:16 or having at least 40% similarity thereto.

63. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:1 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:1 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

64. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:3 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:3 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

65. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:5 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:5 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

66. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:6 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:6 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein

from *L. intracellularis* or related microorganism.

67. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:8 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:8 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

68. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:11 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:11 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

69. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:13 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:13 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

70. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:15 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:15 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

71. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:17 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:17 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein

from *L. intracellularis* or related microorganism.

72. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:18 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:18 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

73. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:19 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:19 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

74. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:20 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:20 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

75. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:21 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:21 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein from *L. intracellularis* or related microorganism.

76. An isolated nucleic acid molecule comprising a nucleotide sequence as set forth in SEQ ID NO:22 or a nucleotide sequence having at least 40% similarity to the nucleotide sequence set forth in SEQ ID NO:22 and which is capable of hybridizing thereto under low stringency conditions and which encodes an immunogenic peptide, polypeptide or protein

from *L. intracellularis* or related microorganism.

77. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:1 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:1 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

78. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:3 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:3 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

79. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:5 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:5 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

80. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:6 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:6 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

81. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:8 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:8 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective

immune response against *L. intracellularis* or related microorganism.

82. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:11 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:11 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

83. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:13 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:13 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

84. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:15 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:15 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

85. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:17 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:17 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

86. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:18 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:18 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a

protective immune response against *L. intracellularis* or related microorganism.

87. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:19 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:19 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

88. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:20 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:20 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

89. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:21 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:21 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

90. A genetic vaccine comprising a DNA sequence having a nucleotide sequence set forth in SEQ ID NO:22 or having at least 40% similarity thereto or is capable of hybridizing to SEQ ID NO:22 under low stringency conditions, said DNA sequence capable of expression in a pig to produce an amount of a peptide, polypeptide or protein effective to induce a protective immune response against *L. intracellularis* or related microorganism.

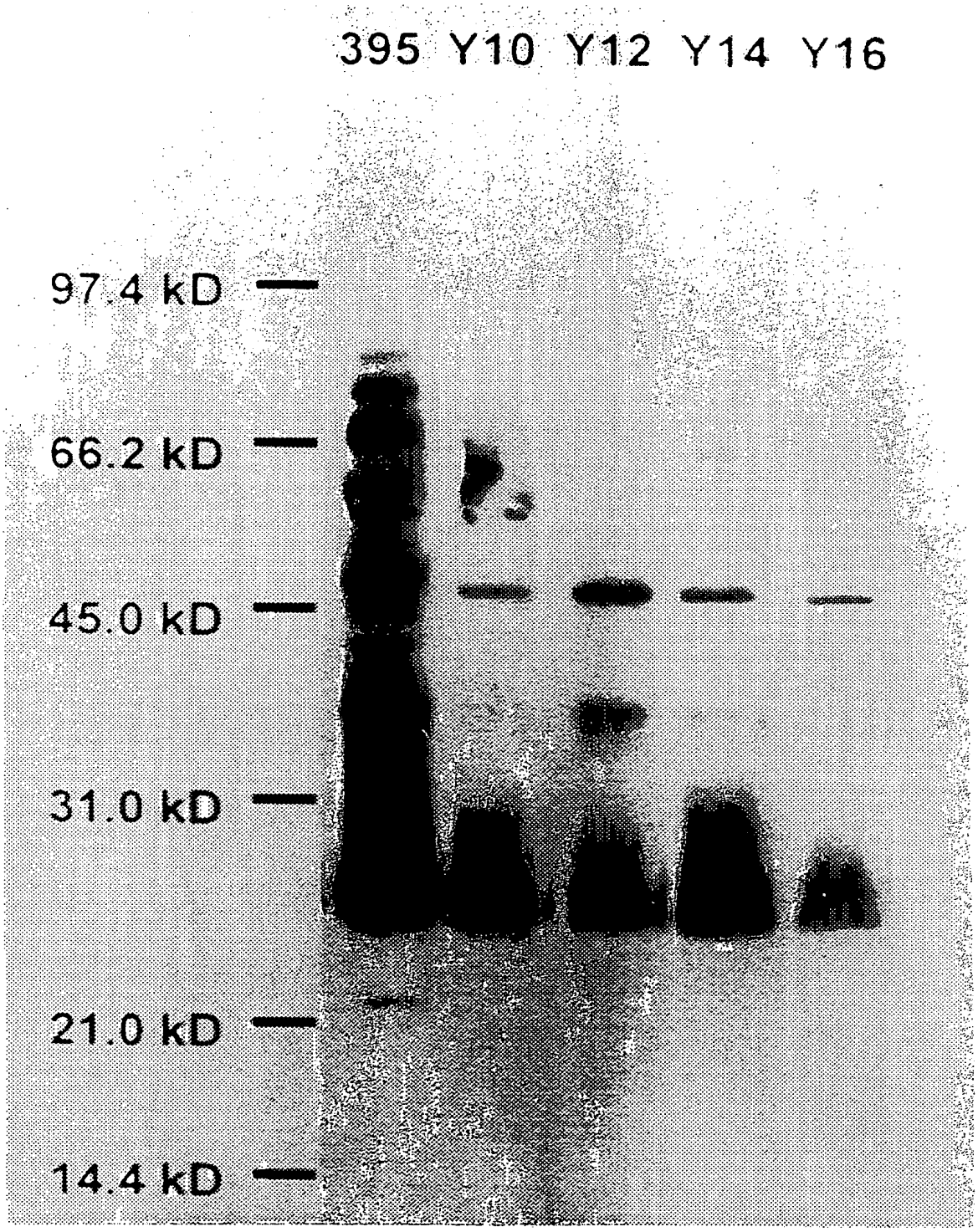

FIG 1

FIG 2

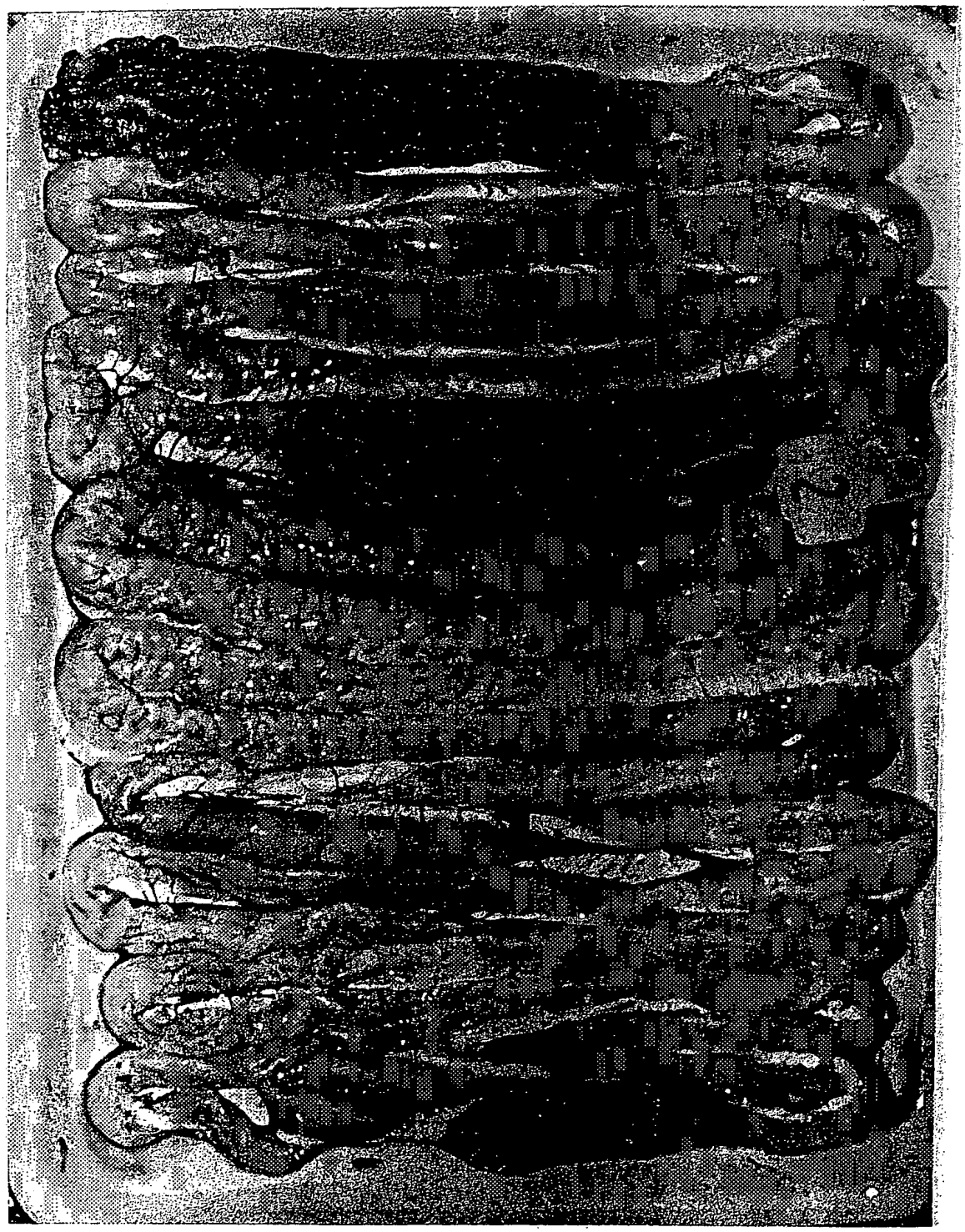

FIG 3

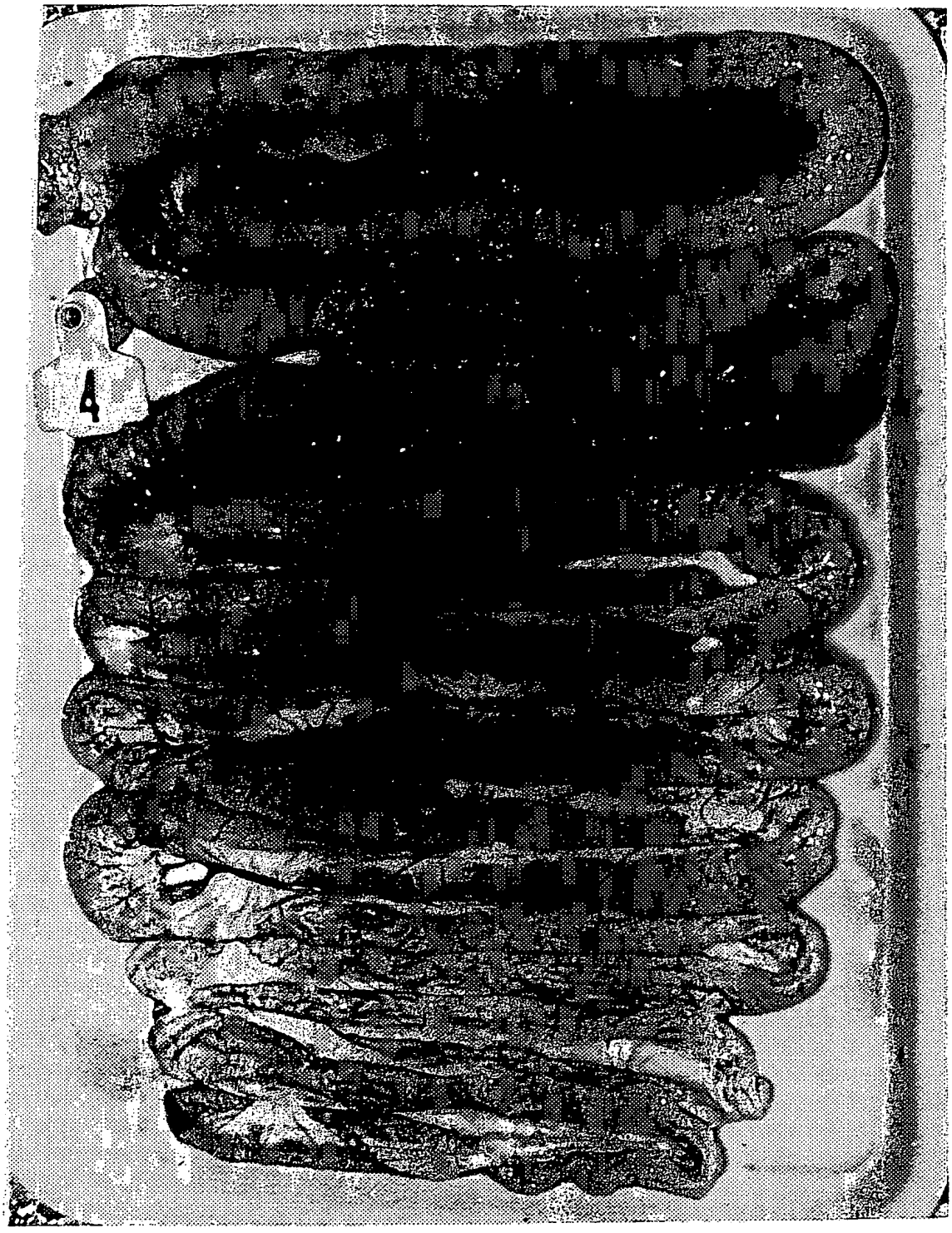

FIG 4

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00767

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C12N 15/31, A61K 39/02, A61K 39/106

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC C12N 15/31, A61K 39/02, A61K 39/106

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU:IPC (as above)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent, Chemical Abstracts: lawsonia, intracellularis, ileal, groel,groes, chaperonin
STN: nucleotide/amino-acid search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU, 69290/94, A (Institut Pasteur et al.) 12 December 1994	1, 2, 6, 7, 10, 11, 63, 64, 77, 78
X	Suerbaum et al., "*Helicobacter pylori* hspA-hspB heat-shock gene cluster: nucleotide sequence, expression putative function and immunogenicity", Molecular Microbiology, Vol. 14, No. 5, 1994, pages 959-974, see entire document.	1, 2, 6, 7, 10, 11, 63, 64, 77, 78

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 1997	26 FEB 1997
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929	Authorized officer **R.L. POOLEY** Telephone No.: (06) 283 2242

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00767

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Kansau et al., "Heat shock proteins of *Helicobacter pylori*", Aliment. Pharmacol. Ther., Vol. 10, Suppl. 1, 1996, pages 51-6, see entire document.	1, 2, 6, 7, 10, 11, 63, 64, 77, 78
X	Wu et al., "Heat Shock- and Alkaline pH-Induced Proteins of *Campylobacter jejuni*: Characterization and Immunological Properties", Infection and Immunity, Vol. 62, No. 10, 1994, pages 4256-4260, see entire document.	1, 2, 6, 7, 10, 11, 63, 64, 77, 78
X	Dunn et al., "Identification and Purification of a cpn 60 Heat shock Protein Homolog from *Helicobacter pylori*", Infection and Immunity, Vol. 60, No. 5, 1992, pages 1946-1951, see entire document.	63, 77
X	Evans et al., "Urease-Associated Heat Shock Protein of *Helicobacter pylori*", Infection and Immunity, Vol. 60, No 5, 1992, pages 2125-2127, see entire document.	63, 77
X	Takata et al., "The Purification of a GroEL-Like Stress Protein from Aerobically Adapted *Campylobacter jejuni*", Microbiol. Immunol., Vol. 39, No. 9, pages 639-645, see entire document.	63, 77
X	Bukanov et al., "Ordered cosmid library and high-resolution physical-genetic map of *Helicobacter pylori* strain NCTC11638", Molecular Microbiology, Vol. 11, No. 3, 1994, pages 509-523.	63, 77

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/AU 96/00767

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU, A	69290/94	WO,	94/26901	EP,	703981	CA,	2144307
		JP,	8510120				

END OF ANNEX

Replaced by Art 34

TABLE 1

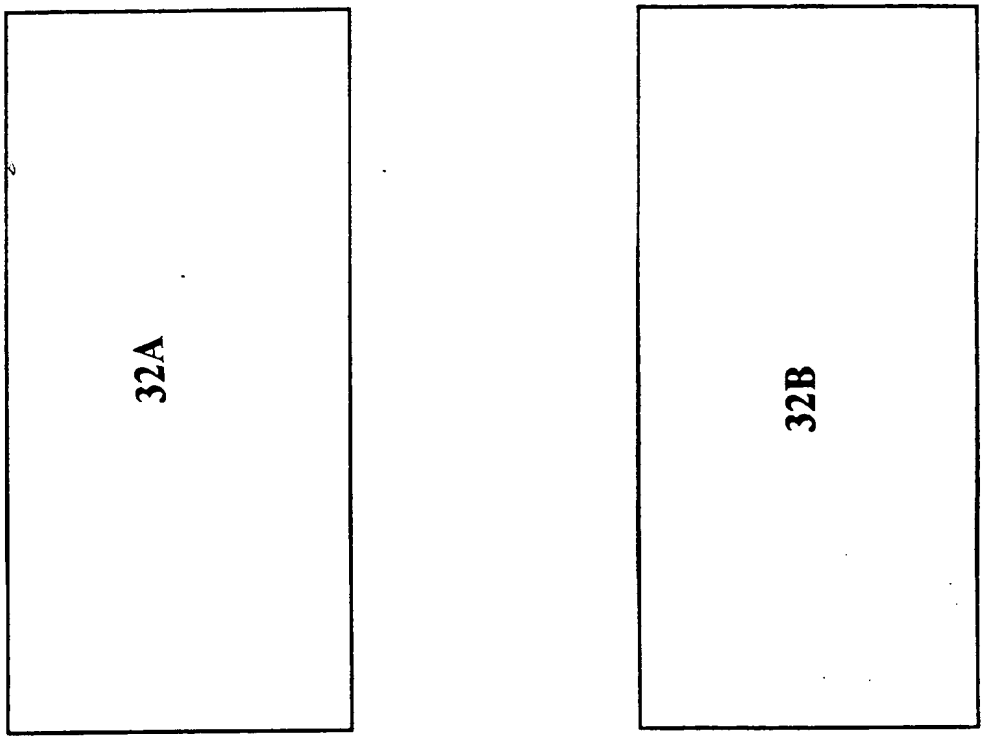

TABLE 1

	Vaccination			Challenge															
	Day -40	Day -33	Day -26	Day -12	Day 0	Day 1	Day 2	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22
1 infected controls								1+	1+	0	0	5+	10+	50+	100+	15	5 cm of thickening		
2 infected controls								0	1+	1+	1+	3+	1+	70+	100+	100	PHE 2.5 M		
3 infected controls								0	0	0	0	0	0	1+	4	16	1+	0	1
4 infected controls								1+	0	0	10+	0	5+	60+	200+	80	PHE 2.0 M		
10 whole bugs		1 ml killed whole cell		1 ml killed whole cell				0	0	0	0	0	1+	1+	0	0	0	0	0

12 whole bugs	1 ml killed whole cell	1 ml killed whole cell	1+	0	0	0	0	2+	0	0	0	0	0	0
14 whole bugs	1 ml killed whole cell	1 ml killed whole cell	0	0	0	0	0	1+	0	<1	<1	0	0	0
16 whole bugs	1 ml killed whole cell	1 ml killed whole cell	0	0	0	0	0	0	0	3	<1	0	0	0
9 Uninfected controls			0	0	0	0	0	0	0	0	0	0	0	0
11 Uninfected controls			0	0	0	0	0	0	0	0	0	0	0	0
13 Uninfected controls			0	0	0	0	Killed Lane							
15 Uninfected controls			0	0	0	0	0	0	0	0	0	0	0	0

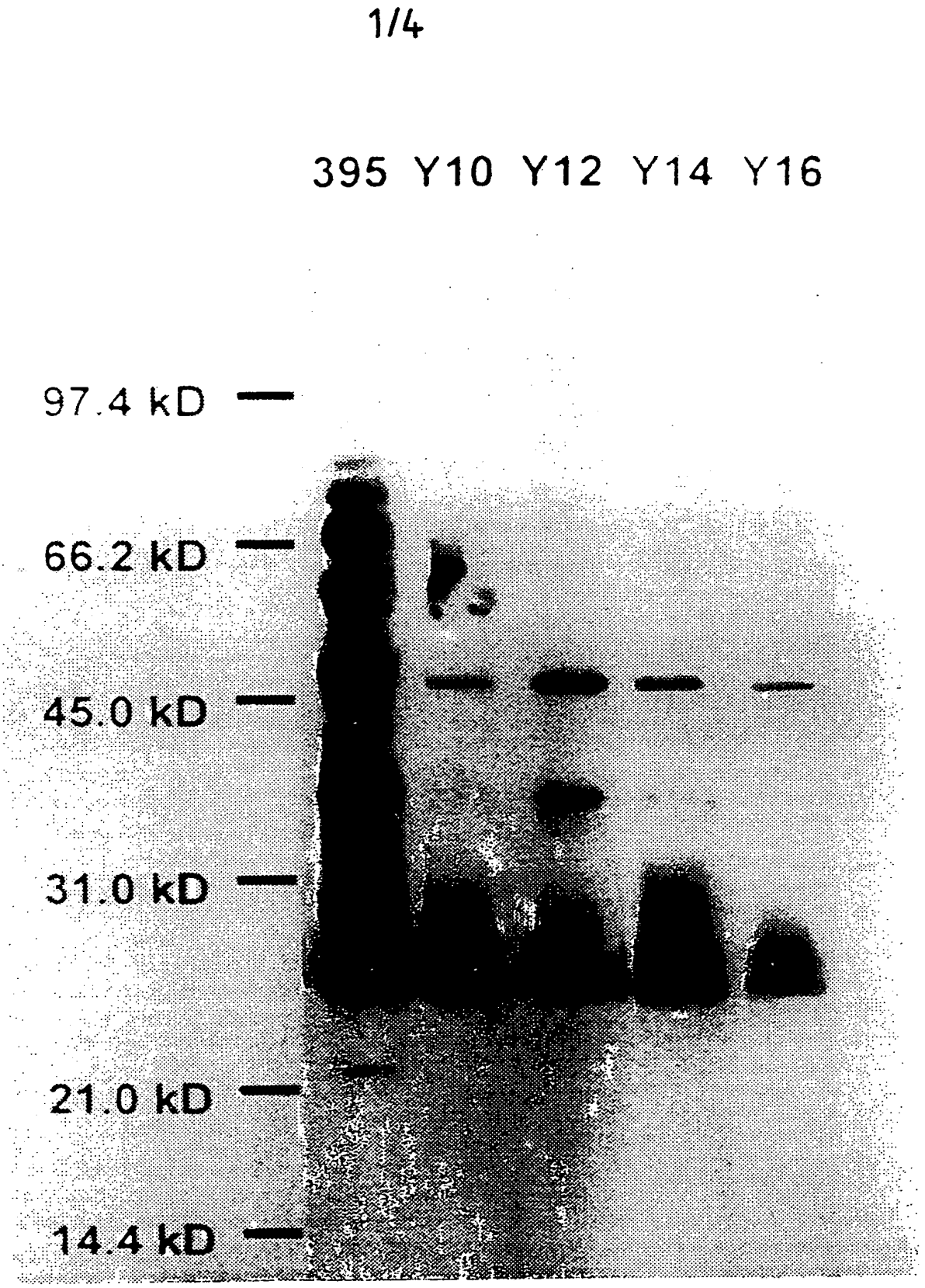

FIG 1

FIG 2

FIG 3

FIG 4